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SYSTEMIC BLASTOMYCOSIS

REPORT OF A CASE

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This case which we believe to be the first reported from the southern states, occurred in the practice of Dr. Robert H. Mitchell and was thought to be an unresolved pneumonia

On Nov. 7 1908 the forty-second day of the illness, and two days prior to death Drs. Fontaine and Haase were asked to see the case. At this time the diagnosis of systemic blastomycosis was made from the appearance of the cutaneous lesions and by demonstrating the organism in the sputum and in the pus

Patient —Mrs. H. aged 27 color white native of Austria married two children one living. Mother died at 70 cause unknown. Father died in old age, cause and time of death unknown. Patient was one of twelve children all of whom are dead save one sister. The last sister to die was sick for some time in Austria with a disease supposed to have been tuberculosis and was nursed almost solely by our patient

History —Shortly after the death of this sister patient emigrated to this country, coming directly to Memphis. She had been in fairly good health until June 15 1908 when she began to cough and to lose weight. This condition was regarded as insignificant and was not treated by a physician. On Aug 1 1908, the cough became worse the sputum was increased and slightly blood-stained. In a few days the sputum became mucopurulent and the patient continued to cough and expectorate until the beginning of her final illness and confinement to bed, which began on Sept. 25 1908

Examination —The patient was first seen by Dr. Mitchell on October 3 one week after the beginning of her final illness and was admitted to St. Joseph's Hospital the same afternoon when the following note of her condition was made. Patient markedly prostrated coughing with expectoration consisting almost entirely of mucus. Temperature 102 3 Respiration 25 Pulse 110 Examination of lungs revealed an area of dulness about two inches in diameter over left upper lobe over which was heard bronchial breathing and increased vocal resonance. The physical signs were those of an ordinary severe lobar pneumonia, but instead of resolution occurring, the disease progressively increased and finally involved the entire left lung

Course of Disease —Throughout the course of the disease the temperature curve was most irregular varying from 97 to 104 F , the highest and the lowest temperature occurring at any time of the day. The pulse for the first two weeks was quite constant about 110. Later it became very rapid and irregular reaching 160 several days before death

Respiration at first showed no marked change from the normal but on the sixteenth day of the disease it began to be more shallow and frequent reaching 64 toward the end of the disease

The urine was examined on October 22, and found normal except for the presence of a few red blood corpuscles The sputum at first consisted of mucus but on the sixth day of the disease it contained blood of a rusty color It was tenacious and was expelled with difficulty Later the sputum became muco purulent, still being slightly tinged with blood it was examined on two occasions for tubercle bacilli and was found negative On the forty second day of the disease it was found to contain numerous blastomycetes no examination for that organism having been made prior to that time

Fig 1 —Lesions in case of blastomycosis from photograph taken two days before death of patient

During the second week of the disease the blood serum responded to the Widal test for typhoid fever

On October 25 an eruption appeared first on the face later on the neck chest back legs and thighs in the order named The first lesion appeared on the forehead as a small papule on the following day it had increased in size and was capped with a pustule it continued to enlarge and others appeared over the regions mentioned until November 7, when the following dermal condition was noted

Scattered over the body were numerous lesions about 600 in all 118 of which were located on the face and head (Fig 1) The lesions varied in size from a pin head to a half dollar the largest the one on the forehead was

oblong in shape dark red in color and raised about an eighth of an inch above the surface and covered with a dirty yellowish crust On removal of the crust an irregular papillomatous surface was noted, with seropurulent fluid between the papillary projections The margin of the growth was moderately infiltrated dark red in color the mass was soft and mushy to the touch and not painful under mild pressure

The large lesions on the lip presented a similar papillomatous appearance, were round smaller and somewhat more raised above the surface than the one on the forehead, they were not surrounded with dark red infiltrated areas All other lesions on the face were raised round red papules covered with a yellowish crust or capped with a pustule varying in size the younger or
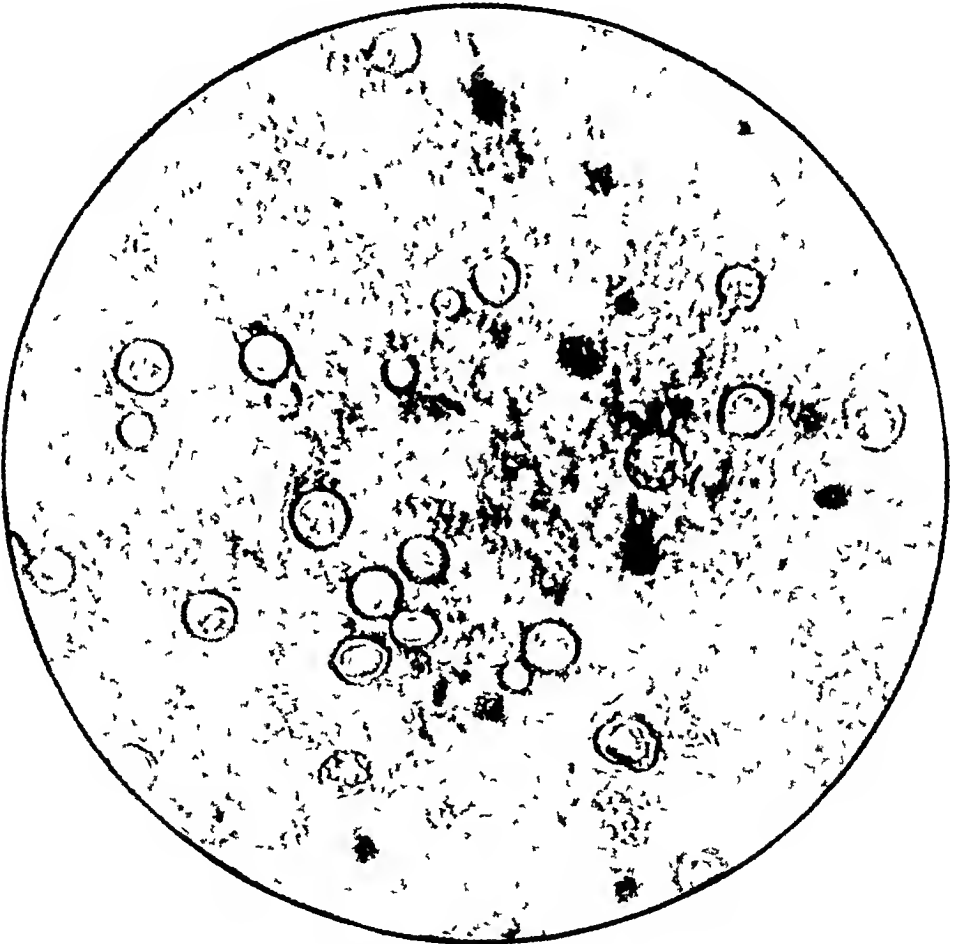
Fig 2 —Smear of pus from skin lesion showing organism, × 500

smaller ones being no larger than a pinhead, but all showing, under the crust or pustule, the same papillomatous condition seen in the older larger lesions

On the anterior portion of the scalp about the median line and one and one half inches posterior to the border of the hair, among smaller ones, there was one large round lesion over which the hair was matted, it was quite soft and from it there was a constant oozing of seropurulent matter

On the hands there were numerous lesions, varying in size and shape, the largest being about the size of a twenty five cent piece, firm, hard, and surrounded by a dark red, raised, firm border and covered with a dark yellow moderately adherent crust On removal of the crust the same condition of the surface was noticed as in those on the face

Fig 3—Right and left lung sectioned

Fig 4—Spleen after section note the enormous number of miliary abscesses

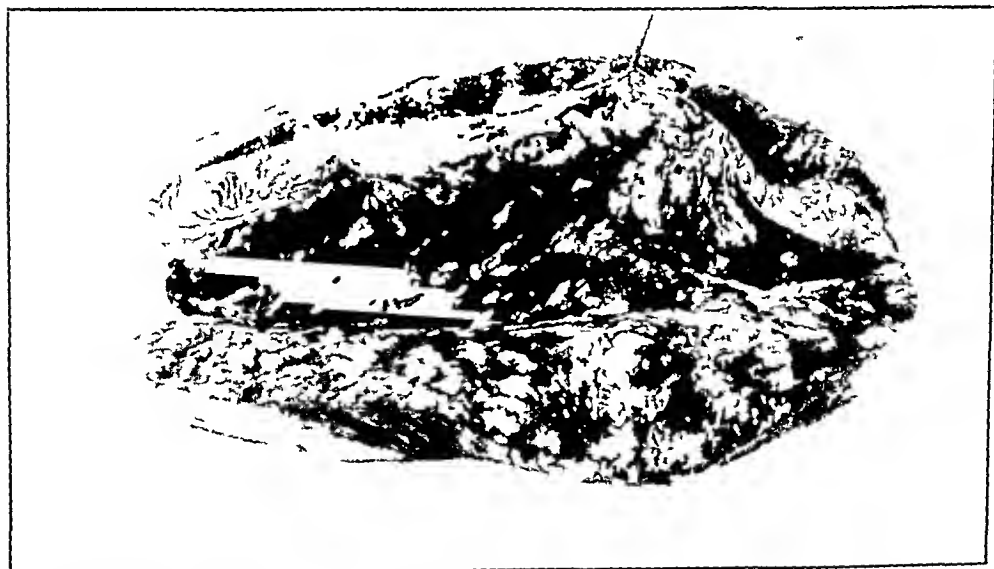The arms trunk and thighs presented numerous lesions none of which was markedly elevated They showed only a faint pink areola with little or no induration differing from the lesions before described to this extent only Otherwise they were similar in that they were capped with a crust beneath which was a pustule invariably presenting the irregular surface with small projecting papillæ from between which the fluid could be pressed

The patient complained of no pain burning or itching from the lesions on the skin
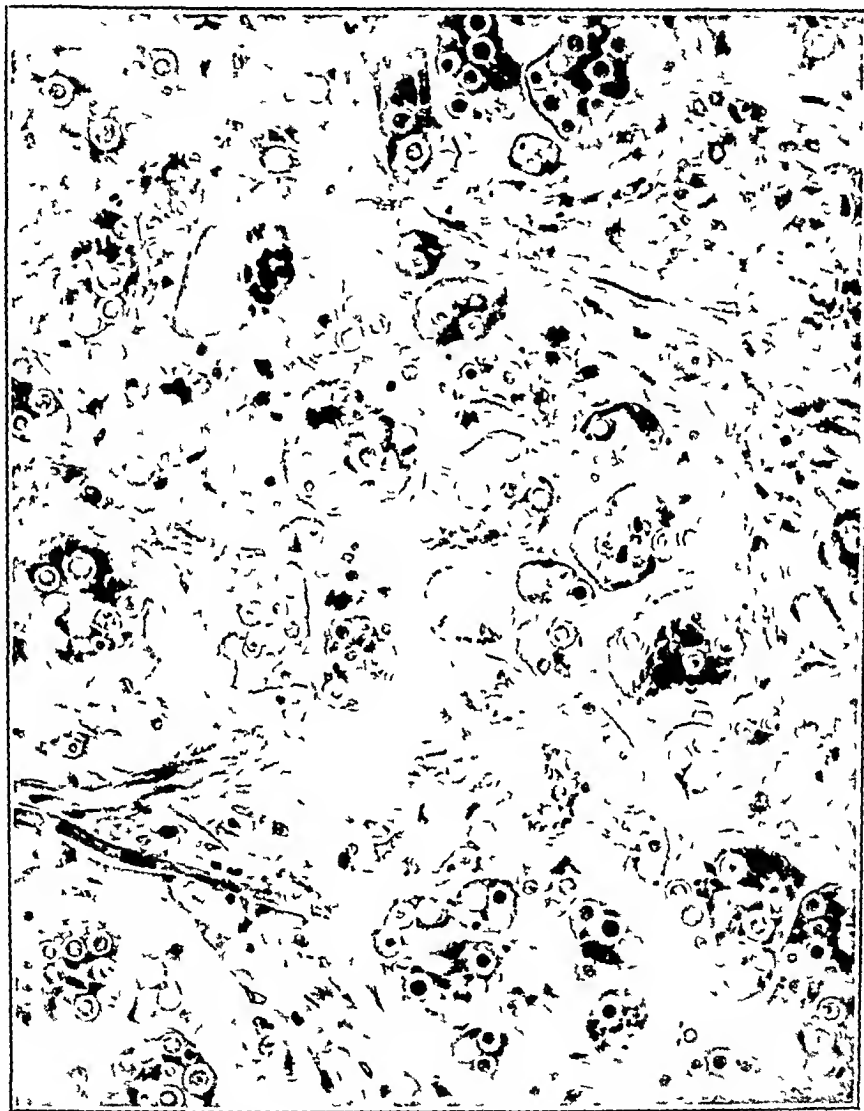
Fig 5 —Section of lung X 150, blastomycetes in large syncytial cell masses

Smears were made from the pus from three lesions and were examined the following morning without staining numerous organisms were found, many of them budding (Fig 2)

None of the lesions was examined microscopically at that time, but at the autopsy three lesions were removed from the face and hands

The patient was given the usual stimulant and supportive treatment besides iodin and several doses of pneumococcic serum Early in the course of the disease moderate doses of potassium iodid were given for several days No improvement was noted and on November 9 death occurred from toxemia

<div align="center">AUTOPSY</div>

This was held two hours after death

Anatomic Diagnosis —Pericardial effusion Catarrhal pneumonia, with miliary and conglomerate abscesses of right lung Pleuritic adhesions Catarrhal pneumonia of lower lobe Necrosis of middle and upper lobes, with miliary and conglomerate abscesses of left lung Parenchymatous and fatty degeneration with acute congestion of the liver Parenchymatous degeneration of the kidneys Acute splenitis, with miliary and confluent abscesses

Fig 6 —Section of lung, × 150, blastomycetes with connective tissue formation and exudation

Macroscopic Examination —Body of an emaciated woman about five feet two inches in length weighing about one hundred pounds Numerous papules, tubercles, pustules and ulcers were scattered over face hands, chest, abdomen back and thighs The lymphatic glands and visible mucous membranes were not involved

Fig 7 —Section of lung, × 225, a, wall of alveolus, b, blastomycetes in tissue, c, exudate in alveoli, d, enormous accumulation of blastomycetes in exudate

Thorax   Pericardial sac contained about six ounces of a clear, straw colored fluid   Heart normal in size, muscles pale and soft, cavities small   Valve leaflets normal and competent   Valve orifices normal in size

Lungs   Left visceral and parietal pleura were united throughout by adhesions which were separated with some difficulty, they were so dense at lung   The lung was distended and heavy   Lower lobe solid and of the consistency of liver   Middle and upper lobes were soft and boggy   The three lobes were densely adherent to each other   The surface was rough and covered

Fig 8—Section of lung × 500   huge masses of blastomycetes

by fibrinous adhesions of a dirty grayish color   mottled with numerous areas varying in size from 1 to 10 millimeters   which were of a yellow color soft and slightly elevated above the surface of the lung   they were not unlike miliary and conglomerate tubercles   On section of the lung the cut surface was of a dirty grayish color   and exuded a thick purulent fluid   (Fig 3)   The upper and middle lobes consisted mainly of confluent areas of soft cheesy necrotic material separated by a small amount of bluish gray lung tissue   The lower lobe contained more lung tissue with a few discrete grayish white soft areas

which had the appearance of beginning necrosis. The bronchi contained a small amount of mucopurulent fluid. Right pleural cavity empty. Right lung distended and heavier than normal, surface smooth and glistening. Posterior part of lower lobe solid, dark red in color and devoid of air, remainder of lung of a bluish-pink color, semisolid and partly crepitant. Over the entire surface of lung were seen grayish slightly elevated discrete areas irregular in shape and varying from 1 to 10 millimeters in diameter. Lobes not adherent to each other. On section the surface had a bluish pink color, was studded with soft yellow areas irregular in shape and sharply outlined from the surrounding tissues and evidently areas of necrosis. The surface exuded a bloody air mixed serum. The bronchi contained some mucopurulent fluid. Smears made from the exudate of both lungs showed blastomycetes in great numbers.

Spleen. Enlarged, measuring 20 by 12 by 10 centimeters. Soft in consistency, dark red in color and thickly studded with yellow slightly elevated areas of

Fig. 9 —Section of liver × 120, c v, central vein, i v, interlobar vessels, liver v vacuole in cells

irregular shape, varying in size from 1 to 10 millimeters. Surface smooth, capsule not thickened. On section, the splenic pulp was found to be dark red in color, interspersed with soft purulent areas of a lemon yellow color, which occupied fully one third of the organ (Fig 4). Smears from purulent areas showed numerous blastomycetes.

Liver. Very much enlarged and soft, surface smooth and pale red in color, capsule not thickened. Cut surface pale and greasy. Lobules indistinct, venules distended. No necrotic areas could be seen. Gall bladder empty, ducts free.

Kidneys. Enlarged, pale red in color, capsule easily stripped, leaving a smooth surface. Cortex and medulla increased in thickness. Glomeruli and

tufts not easily distinguished Venules slightly distended The kidneys presented the appearance of parenchymatous degeneration and did not contain areas of blastomycotic involvement

Stomach, intestines, peritoneum, pancreas, uterus and bladder normal

The brain and cord were not examined

Microscopic Examination—Lungs Under low magnification there was seen a very chronic process in which there was a marked increase of fibrous con

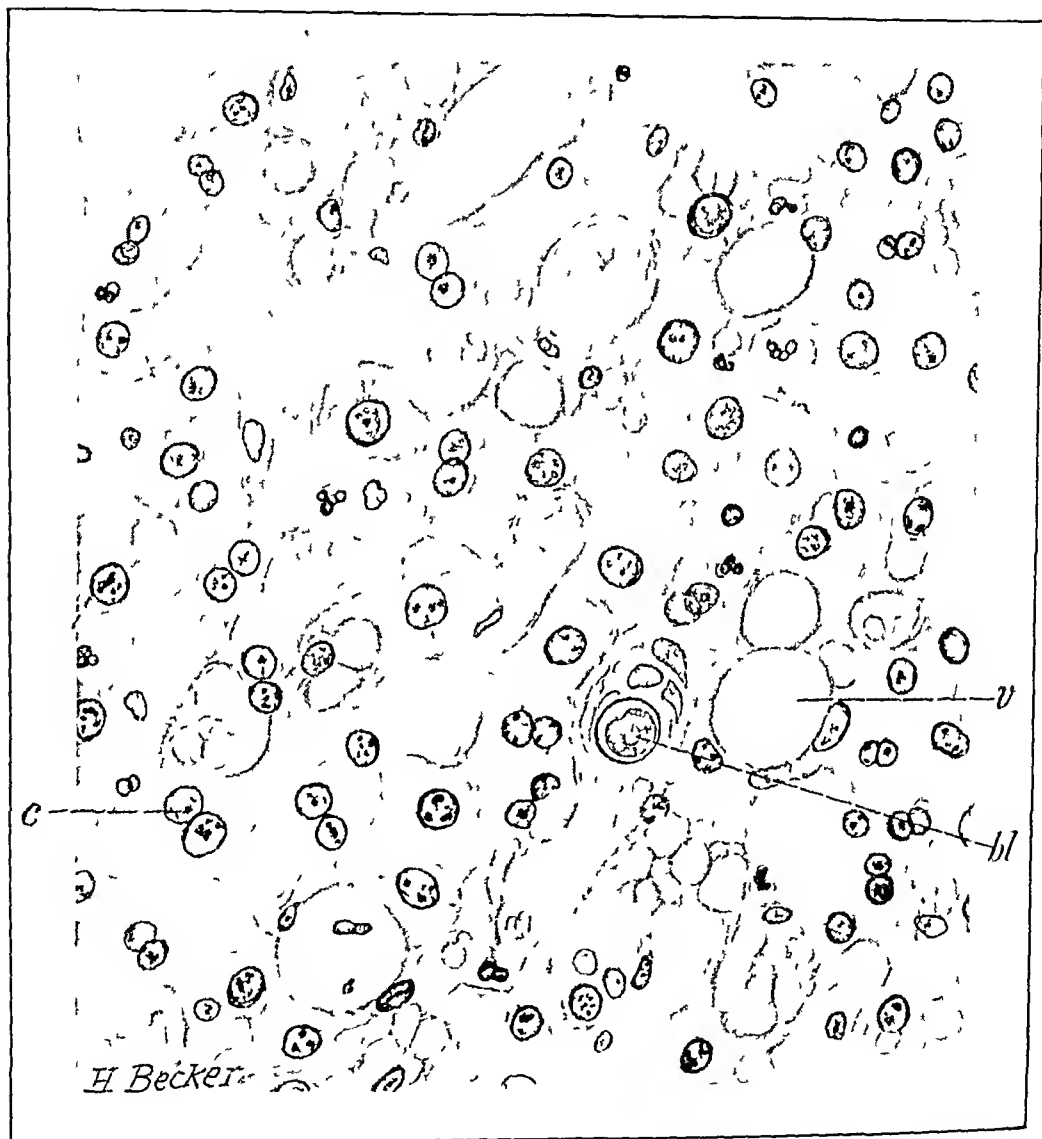Fig 10 —Section of liver, × 575, c, liver cells, v, venole, bl, blastomyces (the only one found in section)

nective tissue in the alveolar walls and about the blood vessels In places, the infiltration was so dense that it almost replaced the lung structure Throughout the fibrous tissue could be seen areas of necrosis and near these necrotic areas could be seen groups of syncytial cells containing blastomycetes (Fig 5)

The more acute process consisted of a pneumonia in which most of the alveoli were seen packed with exudation   Under higher magnification the chronic process could be seen infiltrated with round cells of the lymphoid type   Under high magnification there could be seen slight congestion of the vessels   fibrous infiltration of the alveolar walls and about the blood vessels   The epithelial cells lining the alveoli were swollen and degenerated   In the alveoli the exudation was seen to consist of red blood corpuscles and blastomycetes lying free, polymorphonuclear leucocytes, epithelial cells in process of degeneration and
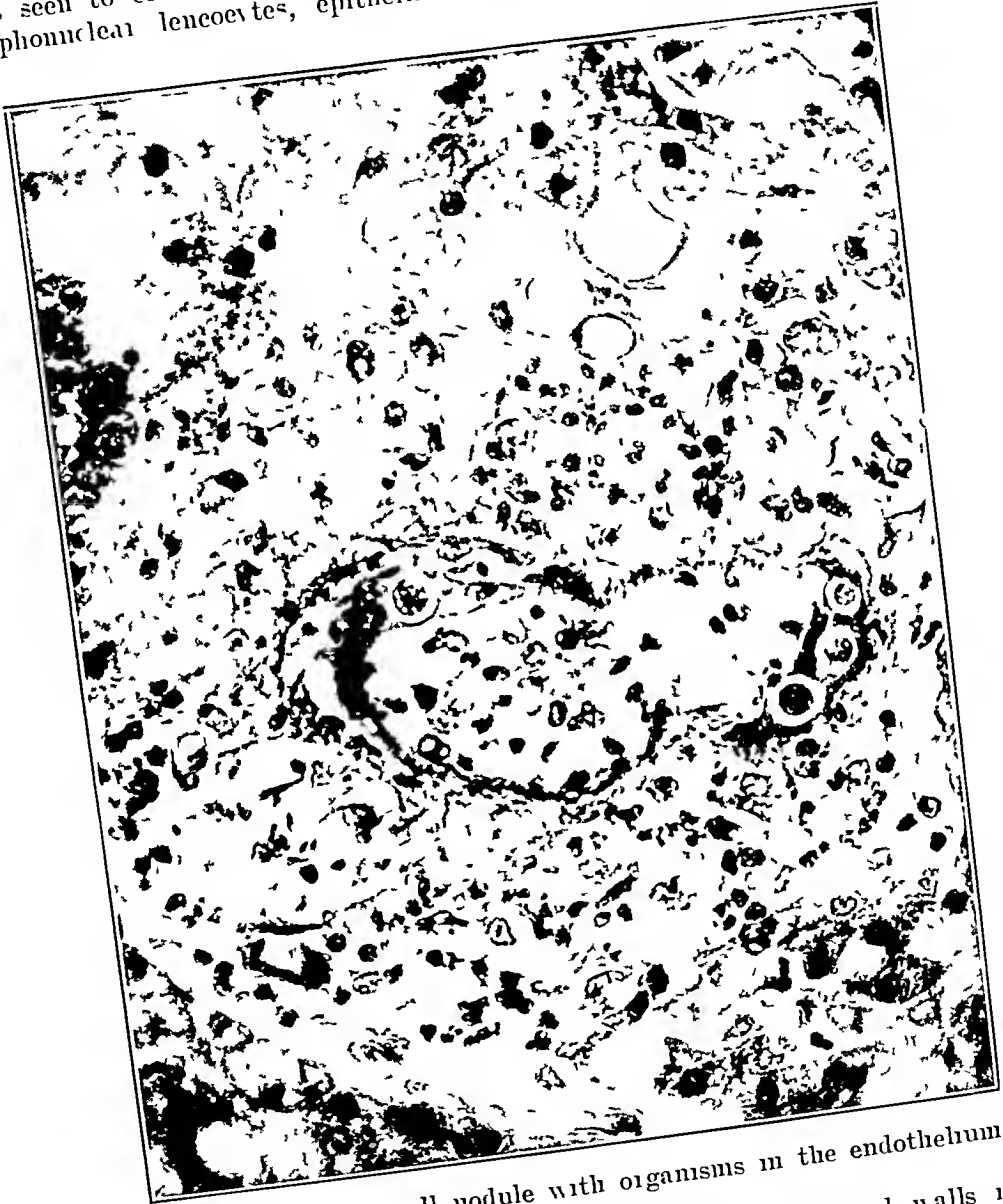
Fig 11 —Liver, small nodule with organisms in the endothelium

threads of fibrin (Figs 6 and 7)   The bronchi had thickened walls in which there could be seen a few blastomycetes, the lumen containing a slight exudate   The lesions in the lungs were remarkable for the extreme fibrosis, the huge number of syncytial cells, and the enormous number of blastomycetes (Fig 8)   Most of the lesions were extremely chronic, but there had been a very acute extension which occurred by way of the bronchi

Liver   Section showed dilatation of the intralobular vein containing a few blood corpuscles, surrounded by an extreme grade of fatty degeneration which
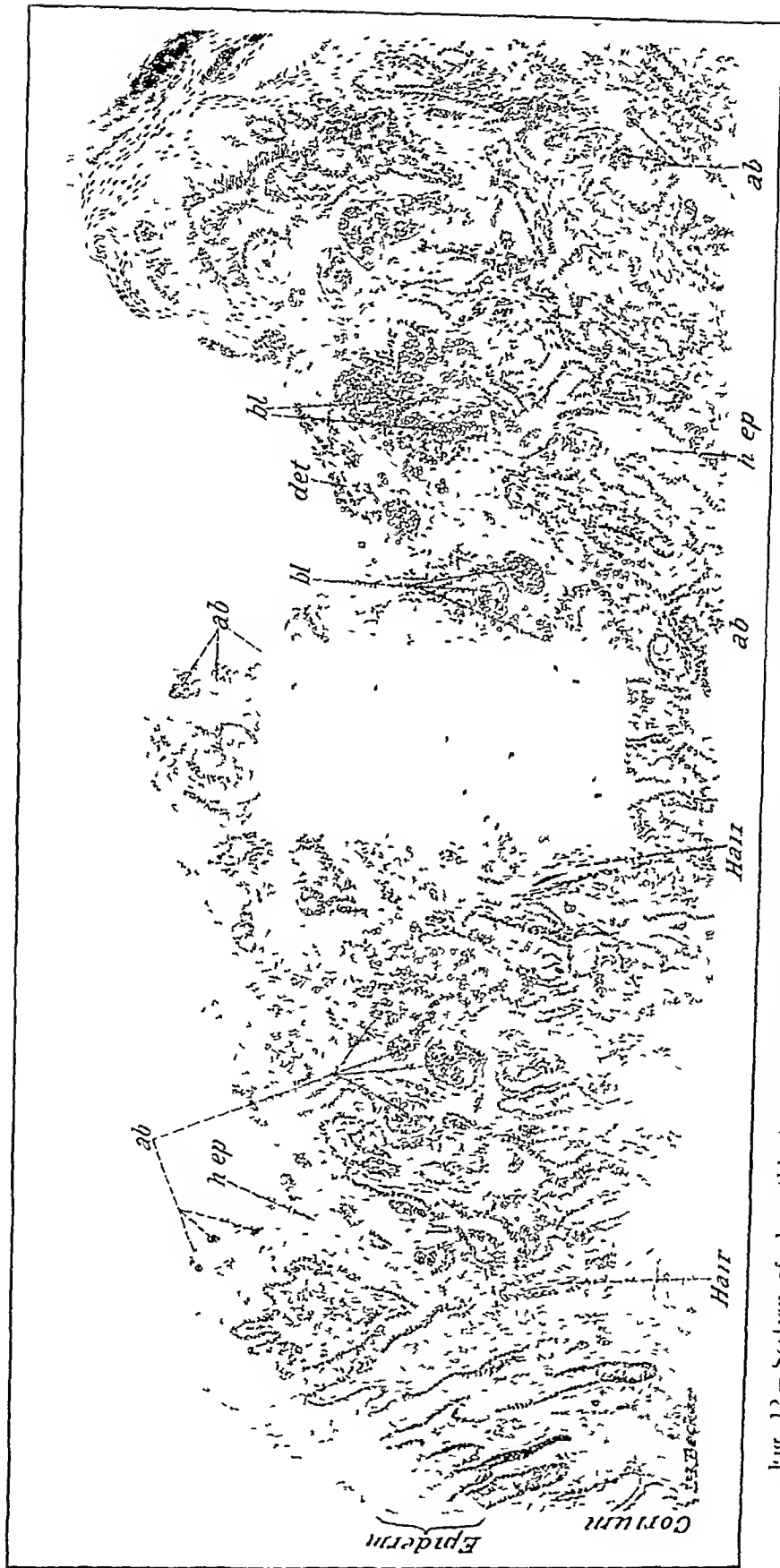
Fig 12.—Section of skin (blastomycosis), 40 times enlarged, h ep, hypertrophied epithelium, ab, miliary abscesses, bl, accumulations of blastomyces, det detritus

extended almost to the periphery of the lobule (Fig 9)   The liver cells in the periphery and about the portal area were slightly degenerated and were separated by a few round cells of the lymphoid type   The vessels about the periphery of the lobule were of normal size (Fig 10)   There were about the intralobular veins a few nodules of blastomycotic infiltration   In the endothelium of the veins there could be seen a few blastomycetes (Fig 11)

Spleen   Malpighian follicles were of normal size and contained areas of hyaline degeneration   There was also slight hyaline infiltration in the intima of the blood vessels and marked proliferation of the cells normally present   There could be seen slight diffuse fibrosis with extravasation of blood throughout the
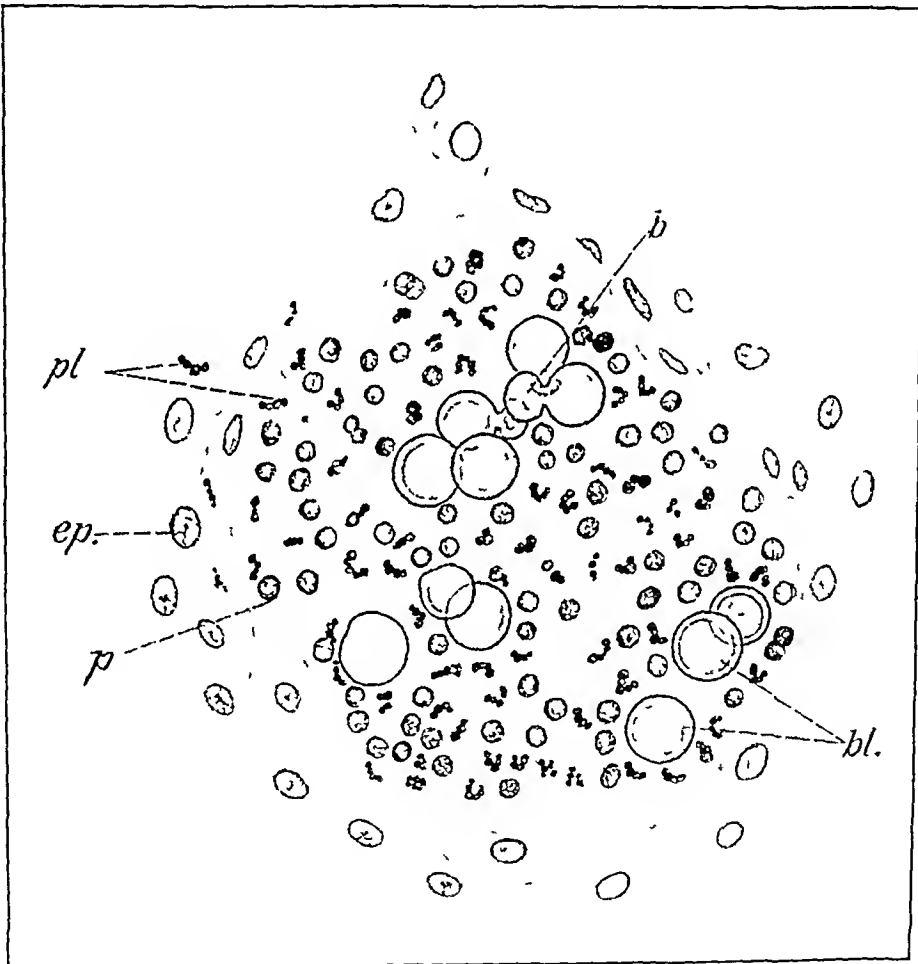
Fig 13 —Abscess in epidermis, ep, epithelial cell , bl, blastomyces, b, budding blastomyces pl, leucocytes p, lymphoid cells

parenchyma   Scattered through the parenchyma were seen miliary abscesses around the abscesses was a slight attempt at encapsulation   The center of abscesses was in a condition of liquefaction necrosis and contained numerous blastomycetes

Kidneys   Epithelial cells lining the numerous tubules were swollen and fragmented   and the nuclei were obscured   The cells contained granular matter and in many places were desquamating   The glomeruli were normal in appearance

Skin   Under low magnification   Beginning from without, there was an ab
sence of the corneous layer and the transitional layers beneath   the prickle
layer was markedly hypertrophied and the cells edematous taking the stain
poorly   Throughout the epidermis small abscesses could be seen   The basal
layer, owing to the hypertrophy, was pushed far into the corium but in all in
stances could be seen intact   The corium showed areas of intense infiltration
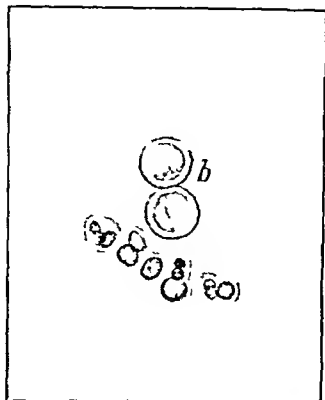
Fig 14 —Skin   b   budding blastomyces   575 times enlarged

with numerous microscopic abscesses   and even under the low magnification
blastomycetes could be seen   (Fig 12)
    Under high magnification the infiltration was seen to consist largely of
round cells instead of the usual plasma cells found in other cases of blastomy
cosis   A few such cells were found only after repeated search   We were unable
to demonstrate any giant cells   The contents of the abscesses were small round

Fig 15 —Epidermis   minute abscess started by a parasite in epithelium,
× 575   bl blastomyces, l leucocyte

cells of the lymphoid type   leucocytes   nuclear fragments and numerous organ
isms (Fig 13)   The abscess walls were composed of apparently normal con
nective tissue fibers with flattened compressed connective tissue cells   The
abscesses were started by the blastomycetes establishing themselves between the
epithelial cells followed by the emigration of polymorphonuclear and lymphoid

cells (Figs 14 and 15) Numerous sinuses filled with organisms could be
seen in the epidermis and corium between the abscesses (Fig 16)

The histopathology of the skin in our case differed from that in those pre
viously reported in that we found only a few plasma cells no giant cells and
great numbers of organisms The organisms in all the lesions were seen to
multiply only by budding and in the sections from the skin and lungs could be
seen buds in various stages of development (Figs 14 15 and 17)

The first case of systemic blastomycosis was described by Busse-
Buschke in 1894 and there have been reported some twenty-three cases
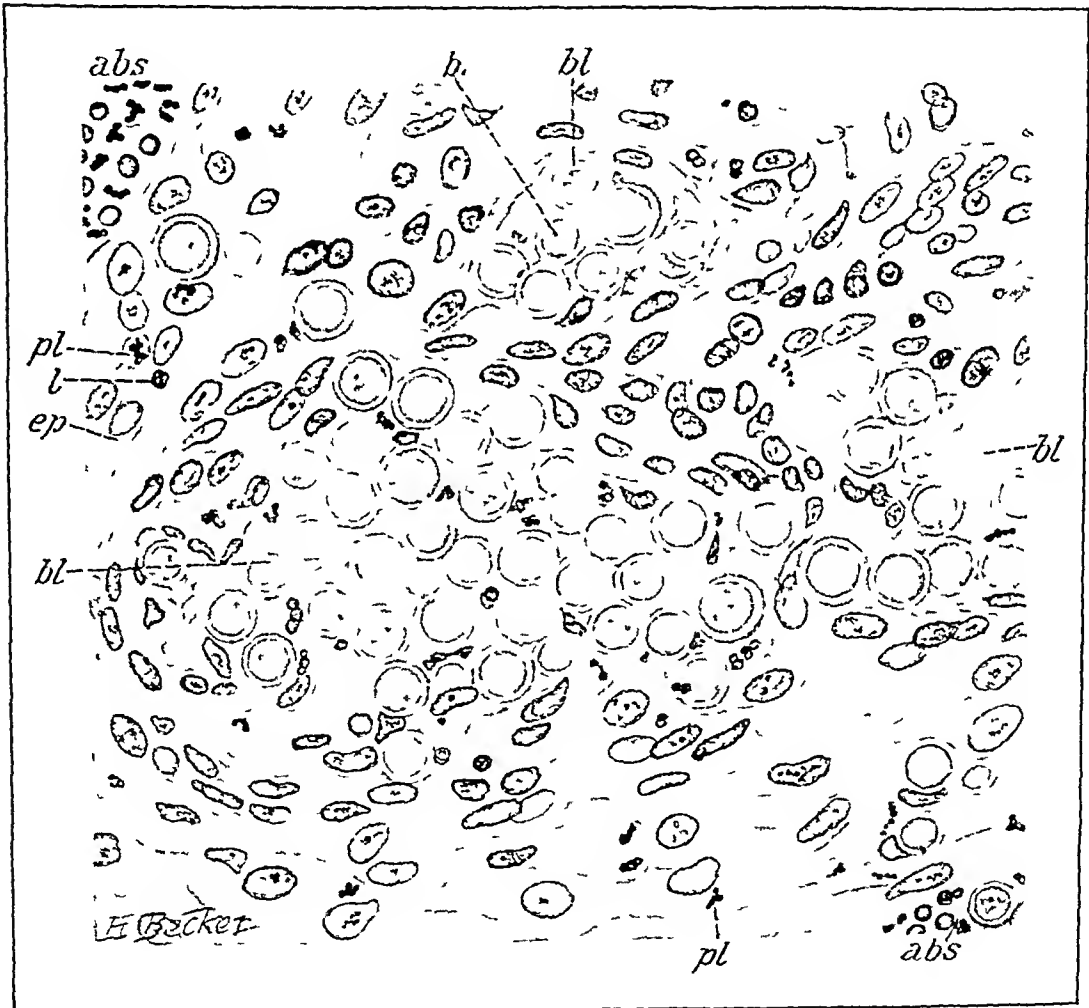
Fig 16 —Blastomyces in a sinus of papilla (skin) enlarged 575 times
ep , epithelial cell, pl , polynuclear leucocyte bl , blastomyces b budding
blastomyces, l , lymphoid cell, abs , abscess

A majority of the cases are reported from Chicago and the most impor-
tant work on the subject has come from that city   A great number of
the cases reported are in foreigners and it undoubtedly exists in every
large city among immigrants

The organisms which are the causative factor of the disease the blastomycetes are vegetable micro-organisms belonging to the yeasts or sprouting fungi. They are oval or round bodies, varying in size from 8 to 12 micromillimeters. They have a doubly contoured capsule, a protoplasm which is finely granular and often vacuolated. Between the

Fig. 17.—Section of lung, × 1000, organisms showing budding

protoplasm and the capsule a clear zone of varying thickness can be seen. The protoplasm is often nearer the capsule at one pole than at the opposite and the clear space varies correspondingly in size.

Reproduction occurs in living tissue by budding and in cultures by mycelial formations.

According to Montgomery and Ormsby, the male sex has furnished a majority of the cases, there being nineteen males to four females among the cases reported in their exhaustive articles [1]

Inasmuch as the lungs were so often primarily affected (in 65 per cent of the cases reported), it is important to consider the respiratory tract as a mode of entrance for the parasite We are quite sure that the disease existed in the lungs in our case for some months before the final illness, and it is more than probable that the illness from which the patient's sister died was the same disease It is easy to confound the disease with tuberculosis Clinically, the two diseases of the lungs can hardly be distinguished except by a microscopical examination of the sputum The gross and microscopic appearance of the lesions are remarkably like those of tuberculosis

Of interest is the fact that the serum from this case responded to the Widal test for typhoid fever, and this is in keeping with the observation of Collins, in which it was found that repeated inoculation of rabbits or goats with brewer's yeast led to the production of agglutinins for the typhoid bacillus and other organisms of the dysentery class

The disease never occurs without cutaneous or subcutaneous lesions The skin lesions are usually secondary, and are metastases from the visceral lesions

The organism can nearly always be demonstrated in the sputum or in the pus from the cutaneous lesions by treating a smear with a 1 per cent solution of potassium hydrate

In our case enormous numbers of blastomycetes were demonstrated in the sputum and in the pus from the cutaneous lesions

We regret that we did not have time to attempt treatment with a vaccine

We are very grateful to Drs Gilchrist, of Baltimore, and Councilman and Pratt, of Boston, for many helpful suggestions in the study of the case

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1   Montgomery, F H, and Ormsby, O S   Systemic Blastomycosis, THE ARCHIVES INT MED , 1908, II, 1

GLANDULAR FEVER

REPORT OF AN EPIDEMIC IN THE CHILDREN'S WARD OF THE UNION PROTESTANT INFIRMARY

J EDWARD BURNS, M D

BALTIMORE

Glandular fever, an acute infectious disease principally affecting the cervical glands, was first described by Pfeiffer in 1889   Since that time various writers, West, Korsakoff, Gourichon Terflinger and others, have reported epidemics and written extensively about it, but conclusions as to its etiology, the portal of entry of the organism causing the infection, the extent of the infection, and the complications arising therefrom are very diverse

The cases reported in this article are nine in number   The first six occurred in children from 2½ to 5 years of age   The last three occurred in the family of Patient 6 after she had left the hospital, and, although not seen in the acute stage, are reported because the clinical history corresponded precisely to that in the cases observed   In this family epidemic only adults were affected   West reported an epidemic of 96 cases occurring in children and Terflinger one of 150 cases occurring in adults, thus showing that this disease, although considered one of childhood, may affect individuals at most any age

The cases reported occurred in the months of February and March and made their first appearance two months after the children's ward had been isolated on account of the measles, scarlet fever and diphtheria in the city   The first case began on February 15, the second on the 16th, the next two on the 17th, and the last two on the 18th

The first case in the family of Patient 6 developed twenty-four hours after the child had reached home   Her mother was the first member of the family affected, none of the family had seen the child for two and a half months previously   From this one would conclude that the incubation period could be as short as twenty-four hours, although most writers think it from seven to nine days

All the cases showed a leucocytosis from 18,800 to 26 400 during the disease   The variations in the differential count during the disease were as follows

	Per Cent
Polymorphonuclear leucocytes .	37 to 74
Small mononucleais	20 to 50
Laige mononuclears	2 to 11
Eosinophiles	0 5 to 5
Transitionals	1 to 7
Mast-cells	0 5

The small mononuclear elements of the blood seem to be the ones principally increased The coexistence of tubeiculous, gonorrheal and chickenpox infections in some of the cases makes the blood picture somewhat confusing

Cases 1 and 2 showed a marked leucocytosis according to the absolute count, yet the differential counts were normal These latter must have been due to an uneven distribution of leucocytes, for it seems very unusual to suppose that all the leucocytic elements of the blood could have been proportionately increased

Leucocytes after convalescence varied fiom 5,000 to 8,000

The vaiiations in differential count aftei convalescence weie as follows ·

	Per Cent
Polymorphonuclear leucocytes	13 to 54
Small mononuclears	30 to 70
Large mononuclears	2 to 14
Eosinophiles	1 4 to 13
Transitionals	1 to 6 5
Mast-cells	0 5 to 2 5

After convalescence there seems to be a still greater relative increase in the small mononuclear elements of the blood

Throats and tonsils of all the patients were injected, but showed no exudate, and the cultures made showed *Staphylococcus auieus*

CASE 1 —The patient, R H , was sent in for treatment of paralysis of left leg due to anterior poliomyelitis Swelling of glands of both sides of neck was first noted on February 15 At this time his temperature was 101 8, pulse 124 The patient complained of tenderness of cervical glands, stiffness of neck, thirst and loss of appetite Enlargement of glands was not confined to the cervical group, of which the upper ones, anterior and posterior to the sternomastoid, were chiefly affected, but the axillary and inguinal groups were also enlarged, although to a much less extent The cervical glands were the only ones tender, and this lasted only three days, after which the swelling began to decrease No abdominal pain or tenderness present The patient was constipated Pharynx and tonsils injected, but no exudate present Throat culture showed *Staphylococcus aureus* On February 16 the white blood count was 26,400 The differential count was as follows

	Per Cent
Polymorphonuclear leucocytes	74
Small mononuclears	22
Large mononuclears	2
Eosinophiles	0 5
Transitionals	1

On February 20 the differential count was

	Per Cent
Polymorphonuclear leucocytes	65
Small mononuclears	20
Large mononuclears	6
Eosinophiles	5
Transitionals	3

Urinary examination showed absolutely no signs of nephritis   The patient left the hospital March 9 before the swelling of glands had entirely disappeared

CASE 2—F R, male, aged 2½ years, epileptic, had swelling of cervical glands of both sides first noted on February 16   On February 15 the temperature rose to 100 6 and on the 16th to 101 6 and then gradually declined

On February 17 the patient's neck was painful and stiff   The soreness lasted one day   After this the glands began to decrease in size, but those on the left are still somewhat enlarged   Axillary and inguinal glands not involved   Pharynx and tonsils injected, the latter enlarged, but showed no exudate   Throat culture showed *Staphylococcus aureus*   No abdominal pain or tenderness   The patient is habitually constipated   There was loss of appetite

On February 16 the white blood count was 22,100   The differential count was as follows

	Per Cent
Polymorphonuclear leucocytes	63 5
Small mononuclears	30
Large mononuclears	2
Eosinophiles	1
Transitionals	2 5
Mast cells	0 5

On February 20 the differential count was as follows

	Per Cent
Polymorphonuclear leucocytes	66
Small mononuclears	25
Large mononuclears	5
Eosinophiles	1
Transitionals	2

The patient is still in the hospital and doing apparently as well as before the attack of glandular fever

CASE 3—L McD, male, aged 3½, had Pott's disease (high dorsal), swelling of cervical glands of both sides first noticed on Feb 17   Axillary and inguinal glands not involved   No rise of temperature   Swelling and tenderness of glands, and stiffness of neck lasted until February 20, after which time the tenderness and stiffness disappeared, and the swelling gradually decreased   The patient held his hands to his ears as if suffering with earache   No abdominal pain nor tenderness   The patient was not constipated, had no sore throat   He had loss of appetite, has had swelling of glands of neck three times previously

On February 20 the red blood count was 4,200,000, white blood count, 21,800, differential count as follows

	Per Cent
Polymorphonuclear leucocytes	44
Small mononuclears	43
Large mononuclears	6
Eosinophiles	3
Transitionals	3
Mast cells	0 5

On March 27 the leucocyte count was about 6,500, the differential count, as follows

	Per Cent
Polymorphonuclear leucocytes	44
Small mononuclears	49
Large mononuclears	5 3
Eosinophiles	1 4

The patient is still in hospital and general condition seems about the same as before he had glandular fever

CASE 4—P K, male, aged 5, had tuberculosis of hip (left) and lumbar kyphosis, swelling of cervical glands of both sides first seen on February 17 Axillary and inguinal groups not involved No tenderness of cervical glands Some stiffness of neck Swelling increased until February 20 and then began to subside On February 17 the temperature rose to 100 and on the 21st to 100 1 It then gradually fell to normal The pulse showed no peculiarities No abdominal pain nor tenderness Pharynx and tonsils somewhat injected but patient complained of no sore throat No exudate present Throat culture showed *Staphylococcus aureus* The patient was not constipated

On February 20 the differential count was as follows

	Per Cent
Polymorphonuclear leucocytes	48
Small mononuclears	38
Large mononuclears	9 5
Eosinophiles	3
Transitionals	3 3

On March 27 the leucocytes were about 5,000, the differential count was as follows

	Per Cent
Polymorphonuclear leucocytes	27
Small mononuclears	49
Large mononuclears	6 8
Eosinophiles	13
Mast-cells	2 5
Transitionals	1

The patient is doing well Cervical glands still somewhat enlarged

CASE 5—M H, female, aged 5, had tuberculosis of hip (left) and chickenpox, bilateral swelling of cervical glands first noted on February 18, no other glandular involvement On this day the temperature rose to 100 8, pulse to 120 The temperature gradually fell to normal by February 23, by which time the tenderness of glands and stiffness of neck had disappeared, and swelling of glands was beginning to decrease The patient complained of earache Pharynx and tonsils injected, but no exudate present Throat culture showed *Staphylococcus aureus* The patient lost her appetite and was constipated No abdominal pain or tenderness

On February 20 the white blood count was 18,800, the differential count was as follows

	Per Cent
Polymorphonuclear leucocytes	37
Small mononuclears	50
Large mononuclears	10
Eosinophiles	2 2
Transitionals	2

On March 27 absolute leucocyte count was about 5,000, the differential count was as follows

	Per Cent
Polymorphonuclear leucocytes	27
Small mononuclears	59
Large mononuclears	6
Eosinophiles	2 5
Mast cells	0 5
Transitionals	4

The patient is doing well   She has entirely recovered from both her chicken-pox and glandular fever without any ill effects

CASE 6 —N S , female, aged 3, had gonorrheal arthritis of hip (left)   On December 29 patient developed tonsilitis, on January 27 left tympanic membrane ruptured due to purulent otitis media, on January 30 patient first showed signs of chickenpox, and on February 18 swelling of cervical glands (left side) was first noted   On February 19 the patient's temperature rose to 101 6, pulse to 144 Cervical glands were tender and neck stiff   Axillary and inguinal glands also somewhat enlarged   By February 23 tenderness of glands had disappeared and swelling was beginning to decrease   At onset pharynx and tonsils were injected Latter were also enlarged   Throat culture showed *Staphylococcus aureus*   There was no abdominal pain or tenderness   Bowels were regular   On February 20 the differential count was as follows

	Per Cent
Polymorphonuclear leucocytes	42
Small mononuclears	40
Large mononuclears	11
Transitionals	7
Mast cells	0 5

Patient left the hospital on February 28 with cervical glands still somewhat enlarged

On March 23 I was told by Dr W S Baer, orthopedist to the Johns Hopkins Hospital, that he had heard that several members of the family of Patient 6, who is a patient of his, had glandular fever   Through the kindness of their family physician, Dr William T Watson, I was permitted to see them   On arriving at their home I found that three members of the family had had what clinically seemed to be glandular fever   The last patient had recovered two days previously, but all showed some enlargement of the cervical glands still   Throat cultures and blood smears were taken from all three and from Patient 6   Culture from the latter showed *Staphylococcus aureus* as before, and differential count was as follows

	Per Cent
Polymorphonuclear leucocytes	13
Small mononuclear leucocytes	70
Large mononuclear leucocytes	14
Eosinophiles	0 5
Transitionals	3

The leucocyte count was about 7 500, and the cervical glands were still slightly enlarged

CASE 7 —The patient, the mother of Patient 6, aged 25, was apparently a healthy woman, she had not seen her daughter for two and a half months and had been perfectly well until the latter's return home on February 28

On the evening of March 1 the patient says she felt tired and ached all over, and on the morning of March 2 both sides of her neck were swollen and painful Her neck was stiff, throat very sore, she had a headache, and ached all over   She

was very thirsty, had no appetite, and was constipated   The neck was swollen and painful for one week, after which time it began to subside   At the onset the patient was nauseated and vomited   No abdominal pain nor tenderness

On March 23 leucocytes were about 5,000, the differential count was as follows

	Per Cent
Polymorphonuclear leucocytes	49
Small mononuclears	34
Large mononuclears	4
Eosinophiles	4
Transitionals	6 5
Mast-cells	0 5

Throat cultures showed *Staphylococcus aureus*   Glands of neck still somewhat enlarged

CASE 8 —The patient, grandmother of Patient 6, aged 50, apparently healthy, on March 13 had headache, ached all over, and had chills   At the same time both sides of neck began to swell and become painful   The neck was stiff and throat very sore   The patient was very thirsty, had no appetite, and was constipated   Swelling and tenderness of glands of neck lasted about one week, after which time it subsided   No abdominal pain or tenderness

On March 23 the leucocyte count was about 7,500, the differential count was as follows

	Per Cent
Polymorphonuclear leucocytes	49
Small mononuclears	41
Large mononuclears	2
Eosinophiles	3 5
Transitionals	4 5

A throat culture showed *Staphylococcus aureus*   Glands of neck still somewhat enlarged

CASE 9 —Patient, maternal uncle of Patient 6, aged 20   General health good   Bilateral swelling of neck first noticed on March 15   At this time patient had a headache and a feeling of general malaise   The neck was stiff and throat very sore   The patient was thirsty, lost his appetite and was constipated   Swelling and tenderness of neck lasted about one week   No abdominal pain or tenderness

On March 23 the leucocytes were about 5,000, the differential count was as follows

	Per Cent
Polymorphonuclear leucocytes	54
Small mononuclears	30
Large mononuclears	12
Eosinophiles	2
Transitionals	3

Throat culture showed *Staphylococcus aureus*   Axillary and inguinal, as well as cervical glands, still somewhat enlarged

In the first six cases the enlargement of the cervical glands occurred at the same time on both sides, with the exception of Case 6, and in the last three cases there was a history of simultaneous enlargement of the glands of both sides of the neck   In only one instance, that of Case 6, was there a unilateral involvement   The swelling of the glands seemed to increase on both sides at the same rate, and with the tenderness seemed

to reach a maximum on the third day, after which time the tenderness disappeared and the swelling began to decrease gradually   The upper glands of the chains anterior and posterior to the sternomastoid muscle were the ones chiefly swollen and tender   All the glands involved were hard and discrete   Stiffness of the neck seemed to disappear with the tenderness of the glands and was due most probably to the latter symptom   The axillary and inguinal group were slightly enlarged and hard in two of the cases   None of the cases showed any signs or gave any history of the occurrence of suppuration of the involved glands

The only definite period of incubation that could be determined with any certainty was that of Case 7, for both the patients in the ward and those on the outside may have become infected at the same time from the same source, or later from other patients   Yet, on account of the varying degrees of individual resistance, the period of incubation would vary greatly   Patient 7 had not seen her child (Patient 6) for two and a half months previously, nor could she remember having been near any one suffering with this disease until she took her child home   This incubation period of twenty-four hours is, as far as I have been able to ascertain, the shortest one recorded

In all the cases observed there was injection of the pharynx and tonsils, but no exudate was present, and all the outside cases gave a history of an intense pharyngitis   This would seem to indicate the probable location of the portal of entry of the organism causing the infection and the finding of *Staphylococcus aureus* in all the throat cultures might mean that this was the etiologic factor   The chief objection to this latter assumption is that in pyogenic infections the blood usually shows an increase in the polymorphonuclear leucocytes, whereas in this infection, as has been shown above, there is an increase in the small mononuclear elements, both during and after the disease   Cases have been reported in which suppuration occurred and its non-appearance in our cases could not be used as an argument against the pyogenic theory of infection

A feeling of general malaise with, in some cases, a slight rise of temperature on the day preceding the enlargement of the cervical glands were the first symptoms noted   Later stiffness of the neck, swelling and tenderness of the cervical glands, thirst, loss of appetite and constipation were the most constant symptoms   Patient 8 had chills at the onset   Nausea and vomiting occurred at onset in Case 7 and this, excepting the constipation which occurred in nearly all the cases, was the only symptom indicating that possibly the disease might be due to an autointoxication from the intestinal tract, as has been thought to be

the case by some writers   None of the patients had any abdominal pain or tenderness

The pulse showed nothing beyond an increase in rate in some of the cases, the volume tension, force and rhythm being unchanged   The temperature varied from 101 8 F to normal at the onset, and in cases of a rise fell by lysis   In the case of the tuberculous patients whose temperature curve was not normal the superadded infection made very little, if any change

The urine was examined where it was possible and showed absolutely no signs of nephritis, either during or after the disease, in fact, no change in its condition from what it had been previous to the infection was noted

NOTE —The following articles may be found of interest on this subject
Gourichon   Thèse de Paris, 1895
Arch Pediat , 1896, xiii, 889
Jahrb f Kinderh , 1889, xxiv, 257
Arch f Kinderh , 1905, xli and xlii
Ztschr f klin Med , 1907, lxii, 170-178
Monchau-Beuchant   Pédiatrie prat , 1908, ii, 223-227
Kuhner   Kinder Arzt, 1908, xix, 121-125
Werner   Tidsshr f d norske Lægefor , 1908, xxviii, 345 349
Crane   Ohio Med Jour , 1908, iv, 143-149
Terflinger, F W   Epidemic of glandular fever   Jour Am Med Assn , 1908, i, 765
Jones   Amer Jour Med Sc , 1908, new series, cxxxv, 346-351

THE ADMINISTRATION OF TUBERCULIN

E C L MILLER, M D

From the Research Laboratories of Parke, Davis & Co

DETROIT

In the early days of tuberculin therapy the administration of large doses proved so disastrous that its use was almost completely abandoned Now under the leadership of Goetsch, Sahli, Denys, Spengler Wright, Trudeau, and others, it is again coming into vogue, but all seem to be agreed that it must be given in small doses The purpose in giving small doses is to avoid a reaction, which is now recognized as harmful to the patient and as influencing unfavorably the subsequent treatment Sir A E Wright does not pretend to increase his dose systematically, but is content if he can keep the tuberculo-opsonic index of his patient "above normal" Except for Wright, most workers look on the administration of tuberculin as a process of immunization of the patient, and hence as the patient's immunity gradually increases they gradually increase the dose The dose should increase *pari passu* with the immunity of the patient, but, as there is as yet no practical means of measuring the patient's immunity, treatment at this point becomes difficult A working compromise is usually effected by laying out for the patient a series of doses progressively increasing in size to be administered at regular intervals, the effect of each dose being watched most closely and the physician holding himself ready to change the series at any point, so as to adapt it more perfectly to the requirements of that particular patient

To meet the demand for tuberculin in small doses for such cases various manufacturers both German and American have put out serial dilutions so that the physician could obtain tuberculin of a strength adapted to each stage of the course of treatment These dilutions are usually decimal and of the following type

First   dilution, 1 to 1,000   contains 1   cubic millimeter per c c
Second dilution, 1 to 10,000,   contains 0 1   cubic millimeter per cc
Third   dilution, 1 to 100,000   contains 0 01 cubic millimeter per c c
Fourth dilution, 1 to 1 000,000, contains 0 001 cubic millimeter per c c

In using this series the physician would give the patient let us assume as

First   dose, 0 1 c c of the fourth dilution or 1/10,000 cubic millimeter
Second dose, 0 2 c c of the fourth dilution or 2/10,000 cubic millimeter
Third   dose, 0 3 c c of the fourth dilution or 3/10,000 cubic millimeter
  And so on up to the tenth dose, 10/10 or 1 c c of the fourth dilution,
containing 10/10,000 or 1/1,000 cubic millimeter

This amount (1/1000 cubic millimeter) is also contained in 1/10 c c of the third dilution, and hence, to avoid injecting the larger quantities of fluid that would be necessary if the fourth dilution were used for larger doses, a change is made to the third dilution and the series continued as follows

Tenth   dose, 0 1 c c of the third dilution or 1/1,000 cubic millimeter
Eleventh dose, 0 2 c c of the third dilution or 2/1,000 cubic millimeter
Twelfth dose, 0 3 c c of the third dilution or 3/1,000 cubic millimeter
  And so on up to the twentieth dose, 10/10 or 1 c c of the third dilution,
10/1,000 or 1/100 cubic millimeter, when a change is made to the second
dilution and so on

On the face of it this would seem to be a series that covers the ground nicely from the lowest to the highest desired dose As a matter of fact, there are objectionable features in this series, which it is the purpose of this paper to point out

The character of the series is best shown by plotting it as a curve using the days of treatment for a base line and doses for ordinates Such a curve is shown in Figure 1, where the numbers on the base line represent days numbered consecutively from the beginning of treatment and the ordinates represent doses expressed in fractions of a cubic millimeter Dots on the curve represent injections It is assumed that an injection is given every five days and that the series is followed as laid out, the curve covering an interval of 100 days and the doses ranging from 1/10 000 to 2/100 cubic millimeters

The most striking feature of the curve is that it is not uniformly progressive, but is broken up into portions that differ very much from one another In the first section (A to B) the doses are regularly increased by 1/10,000 cubic millimeter and the total increase is from 0 to 1/1 000 cubic millimeter, the doses being taken from the fourth dilution When the change is made to the third dilution (plotted as the second section B to E) the very first increase (from B to C 1/10 c c to 2/10 c c, 1/1,000 to 2/1,000 cubic millimeters) is 1/1,000 cubic millimeter, or as much of an increase in five days in one jump as had been attained during the previous fifty days and by ten steps The section continues on by uniform increases of 1/1,000 cubic millimeter up to E where another change occurs The whole of the third section could not be plotted for lack of room, but the first step (E to H) is shown and here again we have a similar jump—the increase from E to H (1/100
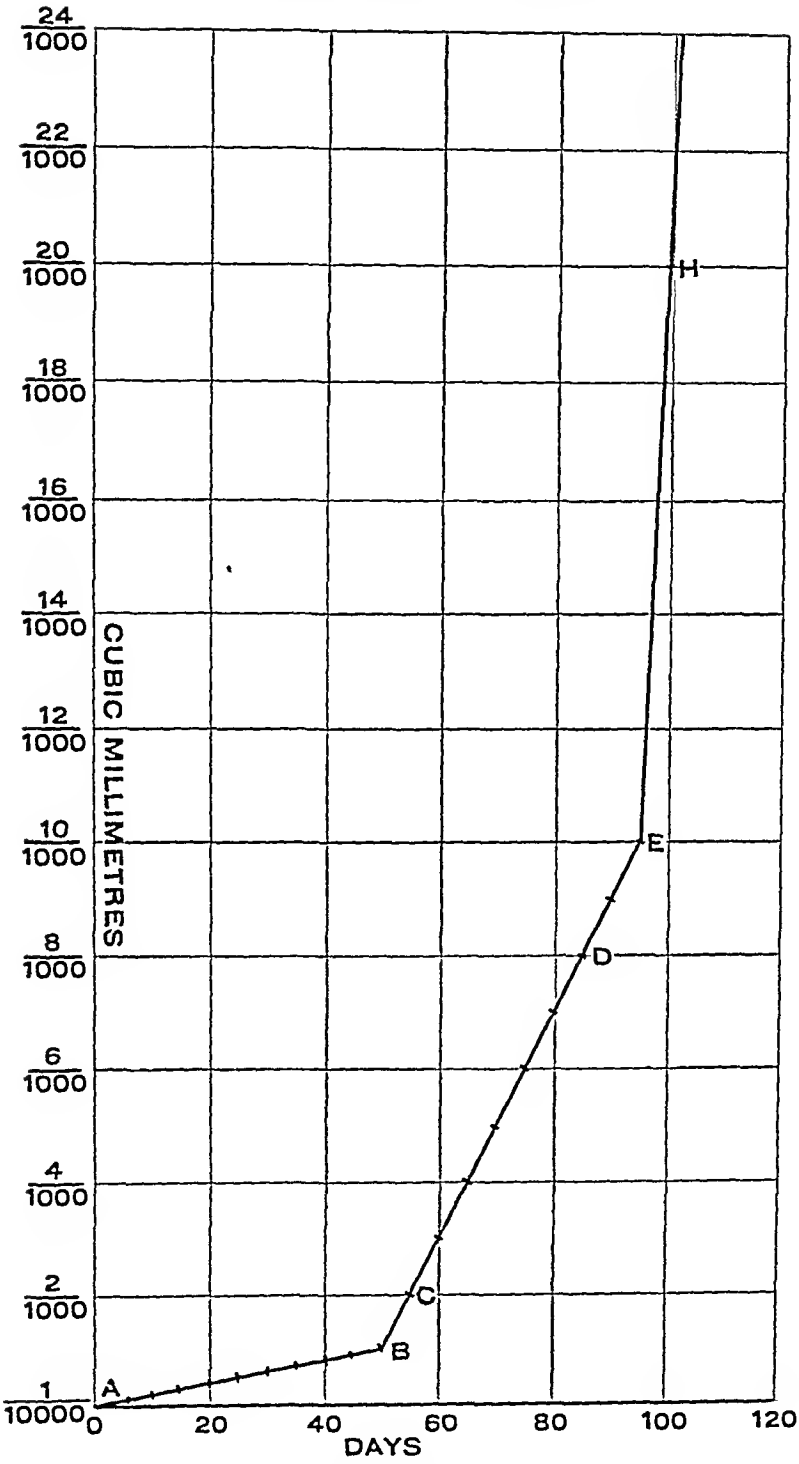
Fig 1—The usual method of administering Tuberculin, curve made up of different arithmetical series, A to B, B to E, etc   The sudden increase of dose from E to H is ten times the constant increase in section B to E, while B C is ten times the increase in A B   Interval between doses, five days

cubic millimeter) being as great as the entire previous increase since the beginning of treatment (0 to 1/100 cubic millimeter), which has occupied ninety-five days and had been divided into nineteen doses

Such a series as this certainly does not offer the uniformly progressive series of doses desired for administration to a patient so that the doses may increase *pari passu* with the resistance of the patient On the contrary, we are inclined to believe that the sudden increase of doses with each new dilution is perhaps responsible for many of the unaccountable reactions, which it is so desirable to avoid in tuberculin therapy, "unaccountable' because these jumps are not manifest when shown in figures, but only when plotted as a curve

To obtain a uniformly progressive series of doses such as we desire it is necessary to use a geometrical progression instead of an arithmetical progression Such a curve is shown in Figure 2, where each dose is 25 per cent larger than the preceding dose It will be noted that there are no sudden jumps in this curve, the interval B' C'' in Figure 2 (1/1,000 to 2/1,000) being covered by three doses instead of the one jump in the corresponding interval (B C) in Figure 1 At the end of the series the conditions are reversed and two doses are required to cover the distance D E, which in Figure 2 is covered in one dose (D' E') When the third series starts the large jump E H, in Figure 1, is covered in Figure 2 by three doses E' H'

It should be understood that in this geometrical curve the ratio (1 25) and the interval (four days) were both chosen to make the curve correspond as nearly as possible to Figure 1 Both curves cover a range of doses running from 1/10,000 to 2/100 cubic millimeters and a period of time of about one hundred days In actual use both the ratio and the interval can be varied indefinitely while still retaining the valuable characteristic of the smooth geometrical progression Some patients may be able to stand an increase of 50 per cent, while for others it may be necessary to cut the increase down to 10 per cent —in the one case the curve would rise more rapidly in the other it would be flatter The interval between doses can be either increased or decreased as desired or it can be made a variable Figure 3 shows a curve similar to Figure 2 except that after every four doses the interval is increased by one day so that the small doses at the lower end of the curve are given at four-day intervals, the large doses at the upper end nine days apart, and the intermediate doses at increasing intervals

Both of these curves are, of course, only suggestive of the type of curve it would seem desirable to follow each patient must be given individual treatment There is however a curve for each case which if
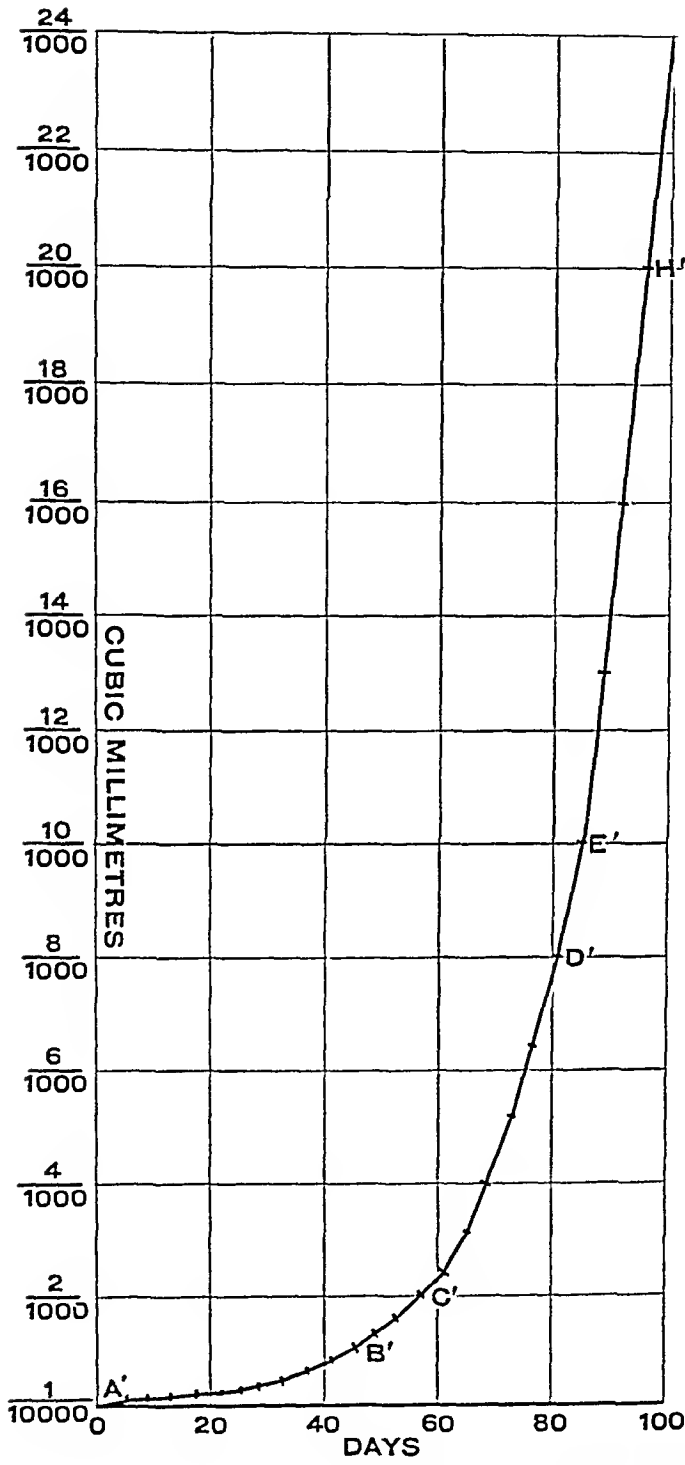
Fig 2 —Curve showing progressive (geometrical) increase of dosage Each dose is 25 per cent larger than the preceding dose and the interval between doses four days
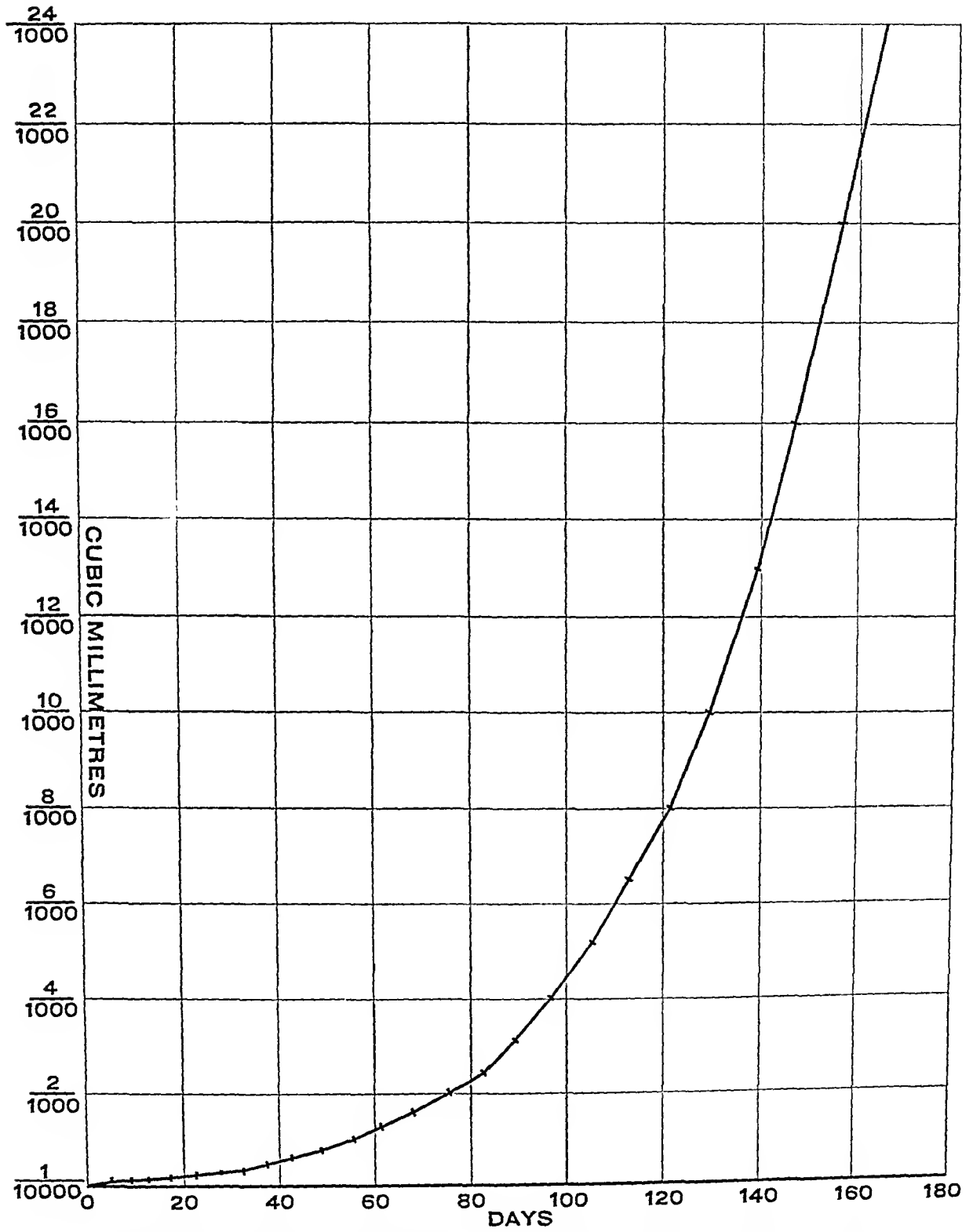
Fig 3 —Curve same as in Figure 2, but after every four doses the interval between doses is increased by one day

followed, will give the best results The trouble is to find it It would seem that the systematic plotting of the treatment of a case week by week as treatment progressed would, by the trend of the curve, be of value in suggesting further treatment or, if a patient when brought up to a certain point showed signs of intolerance and an impending reaction so that it became necessary to interrupt treatment and then begin at a lower point, a curve of the case would show exactly the angle at which the critical point was approached before and would suggest the lower per cent of increase which the patient might be able to keep up indefinitely

The plotting of the curves of cases that have already passed through a course of tuberculin therapy might be instructive The writer would be pleased to receive such curves or the case histories from which the curves could be plotted, and is willing to undertake the work involved in such a plotting in the hope that from a careful comparative study of a large number of cases some light may be thrown on the subject of tuberculin therapy

The problem of obtaining suitable doses for such geometrical series is somewhat difficult, but by no means impossible For a 25 per cent increase the following series is approximately correct   1, $1\frac{1}{4}$, $1\frac{1}{2}$, 2 $2\frac{1}{2}$, 3, 4, 5, 6, 8 and 10   Whether these numbers represent minims or tenths of a cubic centimeter, the first five are too small to be accurately measured This can be overcome by having part of this solution diluted one to four when the first five doses will be 4, 5, 6, 8 and 10 parts respectively, of the one-to-four dilution In this and other ways suitable dilutions can be prepared for any series of doses Physicians without laboratory facilities may find it convenient to have their pharmacists make the needed dilutions for them

To sum up

1 The serial dilutions of tuberculin now available when administered in doses of 1, 2, 3 4, 5 6, 7 8 and 9 tenths of a cubic centimeter or 2 4 6 8, 10 12, 14, 16 18 and 20 minims do not give a uniformly progressive series of doses when passing from one dilution to the next

2 In administering tuberculin each dose should be larger than the preceding by a certain per cent (geometrical progression) rather than by a certain fixed quantity (arithmetical progression)

3 Plotting the treatment of each patient as a curve is advocated because of the light it may throw (a) on the treatment of the individual case and (b) on general tuberculin therapy

TESTS CONCERNING TUBERCLE BACILLI IN THE CIRCULATING BLOOD

E C SCHROEDER and W E COTTON

BETHESDA, MD

On Dec 10, 1908, Dr Randle C Rosenberger of the Jefferson Medical College, Philadelphia, Pa, read a paper before the Philadelphia Pathological Society on the occurrence of tubercle bacilli in the circulating blood The paper was afterward published in *The American Journal of Medical Sciences* for February, 1909 In this paper he recorded that he had made microscopic examinations of the blood of 125 tuberculous individuals, some of whom were affected with only incipient tuberculosis, and that he had found tubercle bacilli in the blood of every one of these individuals In some cases only a few bacilli were seen but, to use his own words, "they were mostly in large numbers and clumps of 30 to 40 bacilli were not unusual, especially in cases of acute miliary tuberculosis" From his observations he formulated the conclusion, "It appears that tuberculosis in all its forms is a bacteriemia"

The occurrence of isolated tuberculous lesions in the bodies of otherwise tuberculous as well as otherwise healthy individuals, located in regions remote from the various channels that communicate with the exterior, gives the belief that tubercle bacilli occasionally float in the blood stream the character of a fact that is hardly open to question The same is true when we consider cases of more or less generalized tuberculosis with many lesions in widely separated portions of the body, and cases of miliary tuberculosis with innumerable lesions of approximately, if not precisely, the same age and stage of development But such occasional presence of tubercle bacilli in the circulating blood is a very different condition from their constant occurrence in it in sufficient numbers to justify the classification of tuberculosis as a bacteriemia Hence Rosenberger s conclusion was received with considerable surprise and decided incredulity

Though the conclusion seems incredible, because it seems nearly impossible that a constant occurrence of tubercle bacilli in the blood of all tuberculous individuals could have been overlooked by the host of investigators who have studied tuberculosis with technic not greatly different from the one he used we did not feel entitled to protest against it without offering some specific evidence to substantiate our protest

Rosenberger stated that he found tubercle bacilli on microscopic examination in the blood of every one of the 125 cases of tuberculosis he studied, notwithstanding that some of the cases were incipient and failed to show tubercle bacilli in the sputum   It was, therefore, almost taken for granted that the microscopic examination of blood, according to his method, of animals affected with advanced and long standing tuberculosis and animals that were expelling tubercle bacilli from their bodies in large numbers, would reveal at least a few tubercle bacilli   A considerable number of such microscopic examinations were made, but not a tubercle bacillus was found in our blood preparations, and we have to record wholly negative results with the blood of tuberculous animals similar to the negative results obtained with the blood of tuberculous persons in two large New York hospitals [1]

It is not uncommon for virulent tubercle bacilli to be present in animal substances in numbers too small to serve for their detection by optical methods   At the experiment station of the Bureau of Animal Industry, for example, we found the intra-abdominal injection of guinea-pigs with suspected milk to be a test for tubercle bacilli that has fully 50 times the delicacy of a microscopic examination   Furthermore, tinctorial and optical methods of distinguishing between tubercle bacilli and other acid-fast bacteria are not wholly satisfactory, hence we decided to inject a sufficient number of guinea-pigs with blood from a sufficient number of certainly tuberculous cattle to show conclusively either that tubercle bacilli are commonly present in such blood or that they are not commonly present in such blood

Incidentally we wish to say that Dr Rosenberger's work is very weak in the extent to which he confirmed, by animal experiments his surprising microscopic observations, which would be of the greatest value if true alone for the early and certain diagnosis of tuberculosis   In all he inoculated only two guinea-pigs of which he gives records—one with blood from a tuberculous person who was expelling tubercle bacilli per rectum and one with blood from a patient with acute miliary tuberculosis

The development of tuberculosis in the latter guinea-pig can not be regarded as a remarkable phenomenon, there is nothing about the fact that a guinea-pig contracted tuberculosis after an injection of blood obtained from a case of acute miliary tuberculosis that necessitates a modification of our currently accepted views on the presence of tubercle bacilli in the circulating blood   That is to say, we need not look on tuberculosis as a bacteriemia because tubercle bacilli were demonstrated

1 Editorial in Med Rec , New York, 1909, lxxv 568

in blood, in which we have long taken their occurrence as a matter of course

This leaves one guinea-pig that may have some evidential value, but we must not lose sight of the fact that it was injected with blood obtained from a person who was expelling tubercle bacilli from his body and, hence, to some extent infecting his environment   We must also bear in mind that guinea-pigs are highly susceptible to tubercle bacilli injected into their bodies and that it is often impossible for an investigator who handles much tuberculous material, who is in frequent contact with tuberculous persons and whose environment may be characterized as containing tubercle bacilli, to eliminate all danger of extraneous tuberculous infection sufficiently to make a test satisfactory when he seeks to verify the tuberculous character of some material from a tuberculous individual by the injection of one, and only one, guinea-pig

Our own tests, which follow, were made entirely with the blood of tuberculous cattle   In every case the blood was drawn from the jugular vein of the tuberculous animal and injected in its fresh, naturally warm state into the peritoneal cavity of a guinea-pig   The tuberculous cattle, as their records show, may be divided into four distinct lots according to the knowledge we have of their tuberculous condition

Lot 1 —Four cattle, the precise tuberculous condition of which is known because they were killed and examined postmortem shortly after the blood was drawn from them for guinea-pig injections

Lot 2 —Six cattle, known to be tuberculous because they had reacted with tuberculin, because tubercle bacilli were found in their feces on microscopic examination and because their feces were proven to be infectious by animal experiments

Lot 3 —Nineteen cattle, known to be tuberculous because they had reacted with tuberculin and because tubercle bacilli were found in their feces on microscopic examination

Lot 4 —Thirteen cattle, known to be tuberculous because they had reacted with tuberculin

We made no attempt to treat the blood used for the injections in any way, because we assumed that the best results would be obtained with it by transferring it as rapidly as possible from the tuberculous cattle to the peritoneal cavities of the guinea-pigs   It was learned from the injections that guinea-pigs tolerate a relatively large quantity of bovine blood in their peritoneal cavity   The guinea-pigs that died shortly after and as the result of the blood injections, about 15 per cent of all injected, with few exceptions showed extreme impaction and some

inflammation of the large bowel, associated in several instances with invagination of the colon

The possibility exists that the intraperitoneal injection of from 3 to 5 c c of fresh, warm blood from tuberculous cattle induces an immunity in guinea-pigs to the tubercle bacilli the blood may contain Though this view is purely hypothetical and we know nothing to sustain it, we have undertaken an investigation to prove or disprove it, and will append the results to this article if they are ready before it goes to the printer

The total number of cattle from which blood injections were made is 42, and these as their records show, represent a considerable variety relative to the severity and extent of the tuberculous disease with which they are affected, from animals that would not have been suspected to be diseased without a tuberculin test to a cow so badly affected that a calf of which she became the mother, a little less than a year before her blood was used for guinea-pig injections, was born affected with tuberculosis contracted from antepartum exposure to her tuberculous body

The total number of guinea-pigs injected was 104   Of these 16 died within a few days after the injection and no doubt as a result of it, 3 died of intercurrent affections, but not until a sufficient period of time had passed for lesions of tuberculosis to become clearly manifest, and 85 guinea-pigs lived until they were killed after a lapse of from seven and one-half to eleven weeks, or an average for all of seventy days after they were injected   The 3 guinea-pigs that died of intercurrent affections showed no lesions of tuberculosis on postmortem examination, and 84 of the 85 guinea-pigs that lived until they were killed showed no lesions of any kind on autopsy   One guinea-pig of the 85 showed lesions very slightly resembling tuberculosis, but these were proved by microscopic examinations and guinea-pig inoculation tests to be free from tubercle bacilli

A detailed record of the cattle and guinea-pigs used in our tests follows

RECORD OF TUBERCULOUS CATTLE AND GUINEA-PIGS

CATTLE, LOT 1

Bull 393, general condition very good, affected with tuberculosis a year or more was killed and examined postmortem on April 8, 1909   The autopsy revealed only one small tuberculous lesion located in one of the superficial inguinal glands

On Feb 5, 1909, two guinea pigs Nos 2891 and 2892, received each an intra abdominal injection of 2 c c of blood from the bull   One guinea pig, No 2891, died on Feb 14 1909, affected with invagination of the bowel   The other guinea-pig remained healthy until April 13, 1909 (sixty seven days after injection), when it was killed and found on postmortem examination to be free from lesions of disease

Cow 533, general condition poor, affected with tuberculosis two years or more, was killed and examined postmortem on April 24, 1909   The autopsy revealed the following conditions, the principal lobe of the right lung contained a cavity about three inches in diameter, partly filled with pasty, necrotic, tuberculous material   This cavity was in direct communication with a large bronchial tube, which contained a considerable amount of material discharged from the cavity   Sprinkled throughout the lungs generally, a number of smaller tuberculous foci, in a completely broken-down condition, were found   The mediastinal and mesenteric lymph glands and the liver were sprinkled with tuberculous foci, some of which were as much as one-half inch in diameter

Prior to the cow's death her feces were examined microscopically on nine different days and on six of these days were found to contain tubercle bacilli

On Feb 3, 1909, two guinea-pigs, Nos 2859 and 2860, received each an intra-abdominal injection of 3 c c of blood of the cow   The guinea-pigs remained healthy until April 13, 1909 (sixty-nine days after injection), when they were killed and found on postmortem examination to be free from lesions of disease

Cow 549, general condition poor, affected with tuberculosis several years, on March 27, 1908, gave birth to a calf affected with congenital tuberculosis   The cow was killed on April 8, 1909, and on autopsy was found to be affected with advanced, generalized tuberculosis   The lungs contained lesions varying from quite recent tuberculous disease to large tuberculous cavities that had discharged most of their contents through the bronchial tubes

No tests were made relative to the infectious character of the feces before death

On Feb 3, 1909, two guinea-pigs, Nos 2863 and 2864, received each an intra-abdominal injection of 3 c c of blood from the cow   The guinea-pigs were killed on April 13, 1909 (sixty-nine days after injection), and on postmortem examination were found to be free from lesions of disease

Cow 552, general condition poor, affected with tuberculosis several years, was killed on April 1, 1909   The autopsy revealed a fairly generalized tuberculosis with lesions of greater or lesser magnitude in the lungs and in the pharyngeal, bronchial and mesenteric lymph glands

Prior to the cow's death her feces were examined microscopically on ten different days, and on six of these days were found to contain tubercle bacilli

Hogs that were fed feces from the cow contracted tuberculosis, and guinea-pigs inoculated subcutaneously with small masses of her feces likewise contracted tuberculosis

Guinea-pigs were injected intra-abdominally with blood from this cow as follows

Jan 25, 1909, Guinea-pig 2785 received 5	c c	of blood
Jan 25, 1909, Guinea-pig 2786 received 5	c c	of blood
Jan 25, 1909, Guinea-pig 2783 received 2 5	c c	of blood
Jan 25, 1909, Guinea-pig 2784 received 2 5	c c	of blood
Jan 25, 1909, Guinea-pig 2781 received 1	c c	of blood
Jan 25, 1909, Guinea-pig 2782 received 1	c c	of blood
Feb 3, 1909, Guinea-pig 2861 received 3	c c	of blood
Feb 3, 1909, Guinea-pig 2862 received 3	c c	of blood
Feb 5, 1909, Guinea-pig 2889 received 2 5	c c	of blood
Feb 5, 1909, Guinea-pig 2890 received 2 5	c c	of blood

Guinea-pigs 2786 and 2890 died prematurely as a result of the blood injections, and the remaining eight guinea-pigs were killed on the following dates and on autopsy were found to be free from lesions of disease

Guinea-pigs 2781 and 2782, killed March 27, 1909 (sixty-one days after injection)

Guinea pigs 2783 and 2784, killed April 13, 1909 (seventy eight days after injection)

Guinea pig 2785, killed April 12, 1909 (seventy eight days after injection)

Guinea-pig 2889, killed April 13, 1909 (sixty seven days after injection)

Guinea pigs 2861 and 2862, killed April 13, 1909 (sixty-nine days after injection)

CATTLE, LOT 2

Cow 511, general condition poor, has been affected with tuberculosis eighteen months or more   Microscopic examinations of the feces on seven different days revealed tubercle bacilli on three days   A hog fed with feces from the cow contracted tuberculosis

On Feb 1, 1909, two guinea-pigs, Nos 2829 and 2830, received each an intra-abdominal injection of 3 c c of blood from the cow   The guinea pigs remained healthy until April 13, 1909 (seventy one days after injection), when they were killed and found on autopsy to be free from lesions of disease

Cow 537, general condition fairly good, has been affected with tuberculosis more than two years   Microscopic examinations of the feces on fifteen days revealed tubercle bacilli on eleven days   Guinea-pigs inoculated with small masses of feces contracted tuberculosis

Guinea pigs were injected, intra abdominally, with blood from the cow as follows

Feb   4, 1909, Guinea pig 2871 received 3 c c of blood
Feb   4, 1909 Guinea-pig 2872 received 3 c c of blood
Feb 19, 1909, Guinea pig 3062 received 3 c c of blood
Feb 19, 1909, Guinea pig 3063 received 3 c c of blood

Guinea pig 2872 died prematurely as a result of the injection

Guinea pig 2871 was killed on April 13, 1909 (sixty eight days after injection), and on autopsy was found to be free from lesions of disease   Guinea pigs 3062 and 3063 were killed on April 13, 1909 (fifty three days after injection), and on autopsy were found to be free from lesions of disease

Cow 538, general condition very poor, has been affected with tuberculosis two years or longer   Microscopic examinations of feces on eleven different days revealed tubercle bacilli on nine days   Guinea pigs inoculated with small masses of feces, and hogs fed feces of this cow, contracted tuberculosis

On Feb 3, 1909, two guinea-pigs, Nos 2851 and 2852, received each an intra-abdominal injection of 3 c c of blood from the cow   On April 13, 1909 (sixty nine days after the injection), the guinea pigs were killed and on autopsy found to be free from lesions of disease

Cow 555 general condition fairly good, has been affected with tuberculosis more than two years   Microscopic examinations of feces on five different days revealed tubercle bacilli on two days   A hog fed feces from the cow contracted tuberculosis

On Jan 30, 1909 two guinea pigs, Nos 2811 and 2812, received each an intra-abdominal injection of 3 c c of blood from the cow   Guinea-pig 2811 died prematurely as a result of the injection   Guinea pig 2812 was killed on April 12, 1909 (seventy-two days after injection) and on postmortem examination was found to be free from lesions of disease

Cow 567, general condition good, has been affected with tuberculosis at least two and a half years   Microscopic examinations of feces on ten different days revealed tubercle bacilli on five days   A hog fed with feces from the cow contracted tuberculosis

On Feb 1 1909 two guinea pigs, Nos 2869 and 2870, received each an intra-abdominal injection of 3 c c of blood from the cow   The guinea pigs were killed

on April 12, 1909 (sixty seven days after injection), and on autopsy were found to be free from lesions of disease

Cow 646, general condition fair, has been affected with tuberculosis for some time, but it is not known just how long Microscopic examinations of feces on two different days revealed tubercle bacilli on one day Guinea-pigs inoculated with her feces contracted tuberculosis

On Feb 2, 1909, two guinea-pigs, Nos 2847 and 2848, received each an intra-abdominal injection of 3 c c of blood from the cow The guinea-pigs were killed on April 13, 1909 (seventy days after injection), and on autopsy were found to be free from lesions of disease

CATTLE, LOT 3

Cow 503, general condition good, has been affected with tuberculosis at least two and a half years Microscopic examinations of feces on two days revealed tubercle bacilli on one day

On Jan 30, 1909, two guinea-pigs, Nos 2805 and 2806, received each an intra-abdominal injection of 3 c c of blood from the cow The guinea-pigs were killed on April 30, 1909 (seventy-three days after injection), and on autopsy were found to be free from lesions of disease

Cow 510, general condition fairly good, has been affected with tuberculosis about three years Microscopic examinations of feces on three days revealed tubercle bacilli on two days

Guinea-pigs injected intra-abdominally with blood from the cow as follows

Jan 29, 1909, Guinea-pig 2791 received 5 c c
Jan 29, 1909, Guinea-pig 2792 received 5 c c
Feb 4, 1909, Guinea-pig 2881 received 3 c c
Feb 4, 1909, Guinea-pig 2882 received 3 c c

Guinea-pigs 2791 and 2792 died prematurely as a result of the injections Guinea-pigs 2881 and 2882 were killed on April 13, 1909 (sixty-eight days after injection), and on autopsy were found to be free from lesions of disease

Cow 512, general condition good, has been affected with tuberculosis eighteen months or longer Microscopic examinations of feces on six different days revealed tubercle bacilli on four days

On Feb 11, 1909, two guinea-pigs, Nos 2823 and 2824, received each an intra-abdominal injection of 3 c c of blood from the cow The guinea-pigs were killed on April 12, 1909 (seventy days after injection), and on autopsy were found to be free from lesions of disease

Cow 513, general condition fairly good, but with greatly enlarged throat glands, has been affected with tuberculosis eighteen months or longer Microscopic examinations of feces on four different days revealed tubercle bacilli on two days

On Feb 2, 1909, two guinea-pigs, Nos 2835 and 2836, received each an intra-abdominal injection of 3 c c of blood from the cow Guinea-pig 2835 died prematurely as a result of the injection Guinea-pig 2836 was killed on April 12, 1909 (sixty-nine days after injection), and on autopsy was found to be free from lesions of disease

Cow 514, general condition poor, has been affected with tuberculosis about three years Microscopic examinations of feces on three different days revealed tubercle bacilli on one day

On Jan 30, 1909, two guinea-pigs, Nos 2815 and 2816, received each an intra-abdominal injection of 3 c c of blood from the cow Guinea pig 2816 died of an intercurrent affection on March 3, 1909 (thirty-two days after injection), and on autopsy was found to be free from lesions of tuberculosis Guinea-pig 2815 was killed on April 12, 1909 (seventy-two days after injection), and on autopsy was found to be free from lesions of disease

Cow 515, general condition fairly good, has been affected with tuberculosis eighteen months or longer   Microscopic examinations of feces on seven different days revealed tubercle bacilli on four days

On Feb 1, 1909, two guinea pigs, Nos 2821 and 2822, received each an intra-abdominal injection of 3 c c of blood from the cow The guinea-pigs were killed on April 12, 1909 (seventy days after injection), and on autopsy were found to be free from lesions of disease

Cow 516, general condition fairly good, has been affected with tuberculosis eighteen months or longer   Microscopic examinations of feces on seven different days revealed tubercle bacilli on four days

On Feb 1, 1909, two guinea-pigs, Nos 2831 and 2832, received each an intra-abdominal injection of 3 c c of blood from the cow The guinea-pigs were killed on April 13, 1909 (seventy one days after injection), and on autopsy were found to be free from lesions of disease

Cow 536, general condition poor, has been affected with tuberculosis two years or longer   Microscopic examinations of feces on eleven different days revealed tubercle bacilli on eight days

On Feb 3, 1909, two guinea-pigs, Nos 2865 and 2866, received each an intra-abdominal injection of 3 c c of blood from the cow   The guinea pigs were killed on April 13 1909 (sixty-nine days after injection), and on autopsy were found to be free from lesions of disease

Cow 561, general condition fairly good, has been affected with tuberculosis two years or longer   Microscopic examinations of feces on nine different days revealed tubercle bacilli on three days

On Feb 1, 1909, two guinea-pigs, Nos 2833 and 2834, received each an injec tion of 3 c c of blood from the cow The guinea-pigs were killed on April 12, 1909 (seventy days after the injection), and on autopsy were found to be free from lesions of disease

Cow 553, general condition fairly good, has been affected with tuberculosis two years or longer   Microscopic examinations of feces on three different days re vealed tubercle bacilli on every day

On Feb 1, 1909, two guinea-pigs, Nos 2827 and 2828, received each an intra-abdominal injection of 3 c c of blood from the cow The guinea-pigs were killed on April 13, 1909 (seventy-one days after the injection), and on autopsy were found to be free from lesions of disease

Cow 620, general condition good, has been affected with tuberculosis a year or longer   Microscopic examinations of feces on four different days revealed tubercle bacilli on one day

On Feb 3 1909, two guinea pigs, Nos 2855 and 2856, received each an intra-abdominal injection of 3 c c of blood from the cow The guinea pigs were killed on April 13 1909 (sixty nine days after the injection), and on autopsy were found to be free from lesions of disease

Cow 629, general condition fair, has been affected with tuberculosis at least one year   Microscopic examinations of feces on five different days revealed tubercle bacilli on two days

On Feb 3, 1909, two guinea-pigs, Nos 2857 and 2858, received each an intra-abdominal injection of 3 c c of blood from the cow The guinea pigs were killed on April 13 (sixty nine days after the injection), and on autopsy were found to be free from lesions of disease

Cow 631, general condition fair, has been affected with tuberculosis at least one year   Microscopic examinations of feces on four different days revealed tubercle bacilli on one day

On Feb 4, 1909, two guinea pigs Nos 2877 and 2878, received each an intra abdominal injection of 3 c c of blood from the cow The guinea pigs were killed

on April 13, 1909 (sixty-eight days after the injection), and on autopsy were found to be free from lesions of disease

Bull 635, general condition good, has been affected with tuberculosis over two years Microscopic examinations of feces on three different days revealed tubercle bacilli on one day

On Jan 20, 1909, two guinea-pigs, Nos 2817 and 2818, received each an intra-abdominal injection of 3 c c of blood from the bull Guinea-pig 2818 died prematurely as a result of the injection Guinea-pig 2817 was killed on April 12, 1909 (seventy-two days after the injection), and on autopsy was found to be free from lesions of disease

Cow 636, general condition fairly good, has been affected with tuberculosis at least one year Microscopic examinations of feces on five different days revealed tubercle bacilli on two days

On Jan 30, 1909, two guinea-pigs, Nos 2803 and 2804, received each an intra-abdominal injection of 3 c c of blood from the cow The guinea-pigs were killed on April 12, 1909 (seventy-two days after the injection), and on autopsy were found to be free from lesions of disease

Cow 638, general condition fairly good, has been affected with tuberculosis over two years Microscopic examinations of feces on four different days revealed tubercle bacilli on all four days

Guinea-pigs were given intra-abdominal injections of the blood of this cow as follows

> Jan 29, 1909, Guinea-pig 2795 received 5 c c
> Jan 29, 1909, Guinea pig 2796 received 5 c c
> Feb 4, 1909, Guinea-pig 2879 received 3 c c
> Feb 4, 1909, Guinea-pig 2880 received 3 c c

Guinea-pig 2795 died prematurely as a result of the injection Guinea-pig 2796 was killed on April 12, 1909 (seventy-three days after the injection), and on autopsy was found to be free from lesions of disease Guinea-pigs 2879 and 2880 were killed on April 12, 1909 (sixty-seven days after injection), and on autopsy were found to be free from lesions of disease

Cow 639, general condition good, has been affected with tuberculosis at least one year Microscopic examinations of feces on four different days revealed tubercle bacilli on one day

Guinea-pigs were given intra-abdominal injections of the blood of this cow as follows

> Jan 29, 1909, Guinea-pig 2801 received 5 c c
> Jan 29, 1909, Guinea-pig 2802 received 5 c c
> Feb 5, 1909, Guinea-pig 2887 received 3 c c
> Feb 5, 1909, Guinea-pig 2888 received 3 c c

Guinea-pig 2801 died prematurely as a result of the injection Guinea-pig 2802 was killed April 12, 1909 (seventy-three days after the injection), and on autopsy several necrotic foci were found in the liver and spleen The lesions were not at all like the conditions caused by the tubercle bacillus and microscopic examinations failed to reveal tubercle bacilli Some of the abnormal tissue was used to make subinoculations into guinea-pigs, the subinoculated guinea-pigs failed to show tuberculosis

Guinea-pigs 2887 and 2888 were killed on April 13, 1909 (sixty seven days after the injection), and on autopsy were found to be free from lesions of disease

Cow 640, general condition good, has been affected with tuberculosis over two years Microscopic examinations of feces on three different days revealed tubercle bacilli on all three days

On Jan 29, 1909, two guinea-pigs, Nos 2799 and 2800, received each an intra-abdominal injection of 5 c c of blood from the cow The guinea pigs were killed

on April 12, 1909 (seventy three days after the injection), and on autopsy were found to be free from lesions of disease

Cow 642, general condition good, has been affected with tuberculosis at least one year   Microscopic examinations of feces on three different days revealed tubercle bacilli on two days

Guinea-pigs were injected intra abdominally with blood from this cow as follows

<blockquote>
Jan 29, 1909, Guinea-pig 2793 received 5 c c
Jan 29, 1909, Guinea-pig 2794 received 5 c c
Feb   5, 1909, Guinea-pig 2885 received 3 c c
Feb   5, 1909, Guinea pig 2886 received 3 c c
</blockquote>

Guinea pig 2794 died prematurely as the result of the injection   Guinea-pig 2886 died on March 5, 1909 (twenty eight days after the injection), of an intercurrent affection, the autopsy revealed no lesions resembling tuberculosis   Guinea pig 2793 was killed on April 13, 1909 (seventy-three days after injection), and on autopsy was found to be free from lesions of disease   Guinea pig 2885 was killed on April 13, 1909 (sixty-seven days after injection), and on autopsy was found to be free from lesions of disease

<div align="center">CATTLE, LOT 4</div>

Cow 479, general condition fair, but with greatly enlarged throat glands, has been affected with tuberculosis about three years

On Feb 4, 1909, two guinea-pigs, Nos 2873 and 2874, received each an intra-abdominal injection of 3 c c of her blood   The guinea-pigs were killed on April 13, 1909 (sixty-eight days after injection), and on autopsy were found to be free from lesions of disease

Bull 508, general condition good, has been affected with tuberculosis about two and a half years

On Feb 4, 1909, two guinea pigs, Nos 2867 and 2868, received each an intra-abdominal injection of 3 c c of his blood   The guinea-pigs were killed on April 12, 1909 (sixty seven days after injection), and on autopsy were found to be free from lesions of disease

Cow 517, general condition good, has been affected with tuberculosis about two and a half years

On Feb 1, 1909, two guinea-pigs, Nos 2825 and 2826, received each an intra-abdominal injection of 3 c c of her blood   Guinea-pig 2825 died of an intercurrent affection on April 5, 1909 (sixty-three days after injection), and on autopsy was found to be free from lesions of tuberculosis   Guinea-pig 2826 was killed April 13, 1909 (seventy one days after injection), and on autopsy was found to be free from lesions of disease

Cow 569, general condition fair, has been affected with tuberculosis about two years

On Feb 1, 1909, two guinea pigs, Nos 2819 and 2820, received each an intra-abdominal injection of 3 c c of her blood   The guinea-pigs were killed April 12, 1909 (seventy days after injection), and on autopsy were found to be free from lesions of disease

Cow 630, general condition fair, has been affected with tuberculosis about one year

On Feb 3, 1909 two guinea pigs, Nos 2853 and 2854, received each an intra-abdominal injection of 3 c c of her blood   The guinea pigs were killed April 13, 1909 (sixty-nine days after the injection), and on autopsy were found to be free from lesions of disease

Cow 632, general condition good has been affected with tuberculosis at least one year

On Jan 30, 1909, two guinea-pigs, Nos 2807 and 2808, received each an intra-abdominal injection of 3 c c of her blood   Guinea-pig 2808 died prematurely as a result of the injection   Guinea-pig 2807 was killed on April 13, 1909 (seventy-two days after the injection), and on autopsy was found to be free from lesions of disease

Cow 634, general condition fair, has been affected with tuberculosis at least one year

On Jan 29, 1909, two guinea-pigs, Nos 2787 and 2788, received each an intra-abdominal injection of 5 c c of her blood   The guinea-pigs were killed on April 12, 1909 (seventy-three days after the injection), and on autopsy were found to be free from lesions of disease

Cow 641, general condition fair, has been affected with tuberculosis over two years

On Jan 29, 1909, two guinea-pigs, Nos 2797 and 2798, received each an intra-abdominal injection of 5 c c of the blood of the cow, and on Feb 4, 1909 two guinea-pigs, Nos 2875 and 2876, received each a similar injection of 3 c c of blood   Guinea-pig 2798 died prematurely as a result of the injection   Guinea pig 2797 was killed on April 12, 1909 (seventy-five days after the injection), and guinea-pigs 2875 and 2876 were killed on April 12, 1909 (sixty-seven days after the injection)   The three guinea-pigs were found to be free from lesions of disease

Cow 644, general condition fair, has been affected with tuberculosis four months or more

On Feb 2, 1909, two guinea-pigs, Nos 2849 and 2850, received each an intra-abdominal injection of 3 c c of blood of the cow   The guinea-pigs were killed on April 13, 1909 (seventy days after the injection), and on autopsy were found to be free from lesions of disease

Cow 645, general condition good, has been affected with tuberculosis three months or more

On Feb 2, 1909, two guinea-pigs, Nos 2845 and 2846, received each an intra-abdominal injection of 3 c c of her blood   Guinea-pig 2845 died prematurely as a result of the injection   Guinea-pig 2846 was killed on April 13, 1909 (seventy days after the injection), and on autopsy was found to be free from lesions of disease

Cow 648, general condition good, has been affected with tuberculosis an unknown period of time   She was brought to the experiment station only shortly before her blood was used for guinea-pig injections and reacted with tuberculin

On Feb 2, 1909, two guinea-pigs, Nos 2837 and 2838, received each an intra-abdominal injection of 3 c c of her blood   The guinea-pigs were killed on April 12, 1909 (sixty-nine days after the injection), and on autopsy were found to be free from lesions of disease

Cow 657, general condition fair, has been affected with tuberculosis an unknown period of time   She was brought to the experiment station only shortly before her blood was used for guinea-pig injections, and reacted with tuberculin

On Feb 2, 1909, two guinea-pigs, Nos 2841 and 2842, received each an intra-abdominal injection of 3 c c of her blood   The guinea pigs were killed on April 12, 1909 (sixty-nine days after the injection), and on autopsy were found to be free from lesions of disease

The 42 cattle included in the records are all those that were available for this investigation among the tuberculous cattle kept for various purposes at the Bureau of Animal Industry Experiment Station   The general condition of the cattle is briefly defined as good, fairly good fair or poor   and as these terms are used somewhat arbitrarily it is desirable to specify more precisely the ideas they are intended to convey

The word "good" is used in connection with cattle that are really in excellent, visible, physical condition and in which no one would suspect disease, the words "fairly good" are used to mean that condition commonly found among dairy cows of the better class, "fair' is used to designate a condition which the average dairyman regards as satisfactory, and the word "poor" is used to qualify all cattle that are thin or that show visible symptoms of disease

Among the 42 cattle 27, or 64.25 per cent, were shown by microscopic examinations to be discharging tubercle bacilli from their bowels, in most instances intermittently, and the infectious character of the feces of 7 of the 42 cattle or 16⅔ per cent, was proved by animal experiments, that is, feeding and inoculation tests

The two facts, that 27 of the cattle were shown by microscopic tests to be expelling tubercle bacilli per rectum and that only 7 were proved by animal experiments to be passing infected feces, must not be taken as being in any sense contradictory, as the feces of only a sufficient number of tuberculous cattle were tested by animal feeding and inoculation experiments to prove conclusively that the acid-fast bacilli found on microscopic examinations in the feces of tuberculous cattle are certainly live, virulent tubercle bacilli

Relative to the expulsion of tubercle bacilli from the bowels of tuberculous cattle, we wish to say that all the evidence we have indicates that the bacilli have their origin in the lungs and throat, from which regions they are coughed up, swallowed, and passed through and out of the intestinal canal without appreciable loss of pathogenic virulence That a large proportion of the tubercle bacilli swallowed by cattle really pass through their bodies and out per rectum, without a determinable loss of virulence, was experimentally shown in some of our earlier work [2] We have absolutely no reason to believe that tubercle bacilli enter the intestinal canal from the lymph radicles or blood capillaries, or by any complex and mysterious system of transportation from lesions of all descriptions and kinds in any or every portion of the body It is our conviction that, unless an open tuberculosis is in more or less direct communication with the intestinal canal or there is a tuberculous disease of the intestine itself, which latter is rare among cattle no tubercle bacilli will be expelled with the feces

If tuberculosis in all its forms was a bacteriemia. the expulsion of tubercle bacilli from the bowels of all tuberculous individuals. as well

2   Bull 88 and 99, Bureau of Animal Industry

as with their urine, saliva, milk and other bodily secretions, would follow as a natural consequence Those who have carefully studied the secretions from the uninvolved organs of tuberculous subjects know how rarely tubercle bacilli are detected in them, even with the application of the most delicate tests

When we consider cattle like Nos 533, 549 and 552, three of the four animals of which autopsy records are given, and note that they were so badly diseased that they would have been condemned on superficial examination as wholly unfit for use as food under the existing meat inspection regulations, the absence of tubercle bacilli from their blood may be regarded as a sufficient reason for assuming that the possible occurrence of tubercle bacilli in the blood of tuberculous animals will almost invariably be associated with pathologic conditions of a very marked character, or that the tubercle bacilli will be present in extremely small numbers and will speedily be filtered out of the blood stream Cow 533 had been affected with tuberculosis two years or longer, was in poor condition as a result of the disease, and on autopsy was found to have an extensive, open tuberculosis of the lung, and lesions of tuberculosis in the liver, and in both the thoracic and abdominal lymph glands Cow 549 was, if anything, even more severely and extensively affected, and less than a year before her blood was injected into guinea-pigs had given birth to a congenitally tuberculous calf Cow 552 was also affected with generalized, advanced, open tuberculosis, and prior to the use of her blood for guinea-pig injections was found to be passing large numbers of tubercle bacilli from her bowels, which were proved by feeding tests to be virulent for hogs, and by inoculation tests to be virulent for guinea-pigs With the blood obtained from these 3 cows 14 guinea-pigs were injected, 12 of which lived two months or more afterward, until they were intentionally killed, when they were found on postmortem examination to be wholly free from lesions of disease of any kind

The possibility exists that tubercle bacilli introduced into the stomach and intestine by swallowing may be taken up by the lymph radicles, passed along the lymph channels and emptied through the great lymph ducts into the venous circulation The investigations of Nicolas and Descos Ravenel, Calmette and Guerin, Schlossman and Engle, and others speak for this but such tubercle bacilli will not be very numerous and will no doubt be filtered out of the blood as soon as it reaches the lung through the heart and pulmonary arteries to which it passes directly after it has received the lymph stream

CONCLUSIONS

We failed utterly to find tubercle bacilli in the blood of tuberculous cattle which we examined microscopically in accordance with the method described and used by Dr Rosenberger

The negative results of our microscopic examinations are confirmed by the negative results obtained with 88 guinea-pigs, each of which received an intra-abdominal injection of blood from a tuberculous cow or bull

As the number of cattle from which blood was injected into the 88 guinea-pigs is 42, and as these cattle represented practically all stages of tuberculosis, from mildly affected, recent cases to old and completely generalized cases, we feel that our work shows beyond the remotest doubt that tuberculosis is not to be classified, in any sense of the word, as a bacteriemia

SUPPLEMENT

In the foregoing article we made the statement "The possibility exists that the intraperitoneal injection of from 3 to 5 c c of fresh, warm blood from tuberculous cattle induces an immunity in guinea-pigs to the tubercle bacilli the blood may contain Though this view is purely hypothetical and we know of nothing to sustain it, we have undertaken an investigation to prove or disprove it, and will append the results to this article if they are ready before it goes to the printer" The results of the additional investigation are now ready and are given in this supplement

On April 24, 1909, blood and tuberculous material were obtained from Cow 533 (see record 8) for a number of guinea-pig injections The primary object of the injections was to prove that the blood of a tuberculous cow, when introduced into the peritoneal cavity of a guinea-pig, has no retarding influence on the development of tuberculosis from tubercle bacilli that may be present in such blood

Cow 533 was first bled from the jugular vein and then at once killed As soon as she was dead a tuberculous mediastinal gland was removed from her body and 500 mg of it emulsified with 2 c c of sterile, normal salt solution Cover glasses of this emulsion, stained with carbolfuchsin and decolorized with 20 per cent sulphuric acid, on microscopic examination revealed, on an average, two tubercle bacilli each The emulsion was mixed with an additional quantity of sterile, normal salt solution, so that each cubic centimeter of the dilution represented a strength equal to one drop of the original emulsion

The blood obtained from the cow prior to her death, and the diluted emulsion made with the tuberculous mediastinal gland from her body, were used to inject seven groups of guinea-pigs, the records of which follow

Group 1 —On April 24, 1909, eight guinea-pigs, Nos 3626 to 3633 inclusive, received each an intra abdominal injection of 3 c c of freshly drawn, warm blood On May 6, 1909, guinea pig 3627 died affected with congestion of the lungs On autopsy no lesions of tuberculosis were found On May 27 and 28, 1909, guinea pigs Nos 3626, 3628 3629, 3630, 3631, 3632 and 3633 were killed and examined postmortem No lesions of tuberculosis or other disease were found

Group 2 —On April 24, 1909, eight guinea-pigs, Nos 3642 to 3649 inclusive received each an intra abdominal injection of 3 c c of freshly drawn blood followed is quickly as possible by an intra abdominal injection of 0 5 c c of tuberculous

emulsion   On April 30, 1909, guinea-pig 3642 died affected with inflammation of the large bowel   On May 27, 1909, guinea-pigs 3643, 3644, 3645, 3646, 3647, 3648 and *3649* were killed and examined postmortem   Every one of the seven guinea-pigs was found to be affected with generalized tuberculosis of the abdominal and thoracic organs

Group 3 —On April 24, 1909, eight guinea-pigs, Nos 3634 to 3641 inclusive, received each an intra-abdominal injection of freshly drawn, warm blood, followed as soon as possible by a subcutaneous injection into the right thigh of 0 5 c c of emulsion   On May 27, 1909, guinea-pigs 3636 and 3637, and on May 28, 1909, guinea-pigs 3634, 3635, 3638, 3639, 3640 and 3641 were killed and examined post-mortem   The eight guinea-pigs all showed more or less extensive lesions of tuberculosis at the seat of the subcutaneous injection, tuberculosis of the adjacent, superficial inguinal gland, tuberculosis of the pelvic, lumbar and gastrohepatic glands and a sprinkling of tuberculous foci in the liver and spleen

Group 4 —On April 24, 1909, eight guinea-pigs, Nos 3658 to 3665 inclusive, received each an intra-abdominal injection of 3 c c of a mixture of defibrinated blood and tuberculous emulsion   Each 3 c c of this mixture was equivalent to 0 5 c c of the earlier described, diluted tuberculous emulsion   The mixture was two hours old at the time it was injected into the guinea-pigs   On April 25, 1909, guinea-pigs 3659, 3660 and 3661 died   The postmortem examination showed no lesions excepting a congested condition of the lungs and a quantity of unabsorbed blood in the peritoneal cavity On May 12, 1909, guinea-pig 3662 died affected with congestion of the lungs, no lesions of tuberculosis were found   On May 27, 1909, guinea-pigs 3658, 3663, 3664 and 3665 were killed and examined postmortem   Three of the guinea-pigs were affected with completely generalized tuberculosis of the abdominal and thoracic organs and one, No 3665, with generalized tuberculosis of the abdominal organs only

Group 5 —On April 26, 1909, eight guinea-pigs, Nos 3670 to 3677 inclusive, received each an intra-abdominal injection of 3 c c of the same mixture of blood and tuberculous emulsion used for the guinea-pigs of group 4   The mixture was forty-five hours old at the time it was injected into the guinea-pigs   On May 27, 1909, guinea-pigs 3670, 3671, 3672, 3673, 3674 3675, 3676 and 3677 were killed and examined postmortem   Seven of the guinea-pigs were affected with generalized tuberculosis of the abdominal and thoracic organs and one, No 3672, with generalized tuberculosis of the abdominal organs only

Group 6 —On April 24, 1909, four guinea-pigs, Nos 3650 to 3653 inclusive, received each an intra-abdominal injection of 0 5 c c of tuberculous emulsion   On May 6 1909, guinea-pig 3651 died affected with congestion of the lungs   On May 27, 1909, guinea-pigs 3650, 3652 and 3653 were killed and examined postmortem Guinea-pig 3650 showed tuberculous lesions of the spleen and omentum only and guinea-pigs 3652 and 3653 showed a fairly generalized tuberculosis of the abdominal and thoracic organs

Group 7 —On April 24, 1909, four guinea-pigs, Nos 3654 to 3657 inclusive, received each a subcutaneous injection, right thigh, of 0 5 c c of tuberculous emulsion   On May 27, 1909, guinea-pigs 3654, 3655, 3656 and 3657 were killed and examined postmortem   Guinea-pigs 3654 and 3656 showed each a small tuberculous abscess at the seat of injection, a tuberculous condition of the superficial inguinal gland near the seat of injection and a fairly generalized tuberculosis of the pelvic and abdominal organs   Guinea-pigs 3655 and 3657 showed similar lesions, with the exception of abscesses at the seat of injection

The guinea-pigs in the seven different groups were injected for the following purposes   Group 1 to serve as checks on the absence or presence of tubercle bacilli

in the blood of the tuberculous cow that was used for the investigation, Group 2, to show that the intra-abdominal injection of fresh, warm blood from a tuberculous cow can not protect against tubercle bacilli simultaneously introduced into the abdominal cavity, Group 3, to show that the intra abdominal injections of fresh, warm blood from a tuberculous cow can not protect against tubercle bacilli into duced into other parts of the body than the abdominal cavity, Groups 4 and 5, to show that the blood of tuberculous cows has no special germicidal potency for tubercle bacilli, and Groups 6 and 7 to serve as guides relative to the amount of tuberculous disease to be expected in the bodies of the guinea-pigs that were injected with both blood and emulsion of tuberculous material

The autopsy records of the guinea pigs show, in a general way, very little difference between the animals that received only tuberculous emulsion and those that received both blood and emulsion   The guinea pigs that received both blood and emulsion into their abdominal cavities showed numerically more extensive lesions of tuberculosis than the guinea-pigs that received only emulsion into their abdominal cavities   This condition would naturally be expected because the same number of tubercle bacilli contained in 3 c c of blood would be more widely separated and in better condition to start a large number of individual lesions than those in 0 5 c c of salt solution

The total number of guinea-pigs injected in this supplemental investigation is 48, of which 8 received blood only, 32 both blood and tuberculous material and 8 tuberculous material only   Of the 32 that received both blood and tuberculous material and the 8 that received only tuberculous material, 6 guinea-pigs died prematurely and the remaining 34, when they were killed, thirty to thirty-one days after the injection, were all found to be affected with tuberculosis of a form that would have progressed to death in a short time

Among the 8 guinea-pigs that received an injection of fresh warm blood without the addition of tuberculous material, 1 died prematurely and the remaining 7 were found on autopsy to be free from lesions of disease   As the cow that supplied the blood for the injections was affected, as her record shows, with extensive, advanced tuberculosis, the 7 guinea-pigs make a strong addition to the 88 parallel guinea pigs of which the records are given in the article to which this supplement is attached, and hence we have 95 guinea-pigs as the total number that received injections of blood from tuberculous cattle into their peritoneal cavities, the most delicate test for tubercle bacilli available and survived the injection long enough for tuberculosis to clearly manifest itself   Among this total of 95 guinea-pigs, not one case of tuberculosis developed

The use of an emulsion of tuberculous tissue from the tuberculous cow that supplied the blood for the supplemental injections was preferred to the use of a pure culture of tubercle bacilli, because it seemed preferable to us to use infectious material and blood in this instance from the same individual case of tuberculosis

The conclusion we draw from our work is this   If tubercle bacilli ever float in the circulating blood of tuberculous individuals, the occurrence is very rare, so rare indeed, that no form of tuberculosis can reasonably be characterized as a bacteriemia [3]

Mohler examined the blood of 8 cattle microscopically and with blood from each of these cattle injected 5 guinea pigs   The microscopic examinations and injections were made precisely in the manner described by Dr Rosenberger   No tubercle bacilli were discovered microscopically and not one of the 40 injected

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[3] An independent investigation relative to the occurrence of tubercle bacilli in the circulating blood of cattle was made at the Federal Bureau of Animal Industry by Dr John R Mohler Chief of the Division of Pathology

guinea-pigs contracted tuberculosis Two of the 8 cattle were in good condition, but were passing tubercle bacilli from their bowels, 2 of the cattle were in poor condition and were passing tubercle bacilli from their bowels, and 4 of the cattle were slaughtered for meat, but on inspection were found to be so extensively affected with tuberculosis that it was necessary to condemn and tank their carcasses under the federal meat inspection regulations

This additional investigation is especially important because the methods used to discover tubercle bacilli in the blood were identical throughout with those used by Dr Rosenberger, and which, in Rosenberger's work, invariably gave positive results

THE RELAPSING FEVER OF PANAMA*

SAMUEL T DARLING, M D

ANCON, CANAL ZONE

Publication of this paper has been withheld by the writer in order that the animal reactions of the new world monkeys might be worked out, and also that further attempts to produce a polyvalent hyperimmune serum might be made, but it is thought that the paper should now be published as it is, as the production of an immune serum can be much better accomplished near a constant and larger supply of laboratory animals

INTRODUCTION

As Novy,[1] Mackie[2] and others,[3] in part, have pointed out, it is possible with the means at present at our disposal to separate the spirochetes causing relapsing fever into four groups, the separation being based on animal reactions specific characters, such as agglutination and immunity, and certain clinical features of the infection in man

This paper deals chiefly with some of the characters of the spirochete causing the relapsing fever of the Isthmus of Panama   The work was done at Ancon Hospital during the period between July, 1907 and February, 1908

Relapsing fever has been reported from time to time in the canal zone since the American occupation in 1904   Most of the cases have been from Colon Hospital about twenty-five in number, and five from Ancon Hospital (Panama)   They have occurred chiefly among white laborers and have been distributed among Italians, Spaniards, Turks, Germans Scotch, Greeks and Americans   The patients have all been seen in the wards where the diagnosis has been made by blood examinations, and they have all presented the classical features of relapsing fever with two or more relapses

*The greater portion of this investigation was read at the Canal Zone Medical Association, Ancon, C Z, Feb 8, 1908

1 Novy, F G and Knapp R E   Jour Infect Dis, 1906, m, 291

2 Mackie F P   N Y Med Jour 1908 lxxviii 337

3 Uhlenhuth and Haendel   Arb a d k Gsndhtsamte 1907, xxvi, h 1 1
    Mantenfel   Arb a d k Gsndhtsamte, xxvii, h 2, 327
    Shellack, C   Arb a d k Gsndhtsamte, xxvii, h 2, 364
    Marchoux E and Salimbeni A   Ann de l'Inst Pasteur, 1903, xvii, 569

Carlisle[4] has given us an excellent summary of the geographical distribution of relapsing fever With regard to America, a few sporadic cases and one epidemic have been reported in the United States, all of them being traced to recently arrived immigrants or sailors Cases have been reported from Tuxpam, Mexico, a seaport between Vera Cruz and Tampico, and from Cuba, Peru, Chile and Bolivia Hirsch[5] in 1881 stated that nothing was known of its existence in Central and South America Dr R Franco[6] of Bogota, U S of Colombia, has discovered a febrile spirochetosis, the spirochete of which, it is said, can not be differentiated from *Sp duttoni Ornithodoros turicatus* is thought to be the species of tick which conveys the disease It may be that the relapsing fever of Panama has been introduced from the United States of Colombia, where it appears to be endemic

There are no records of the disease having been recognized on the Isthmus of Panama previous to 1905 If it appeared here before that date it was probably called "malarial fever" or "typhus fever " In the absence of an absolute diagnostic criterion many cases of relapsing fever in the past must have been confounded with typhus and malarial fevers

It would be disappointing to find in a disease of so wide a geographical distribution as relapsing fever that Hippocrates[7] had not made some clinical observations, and we are, therefore, not surprised to learn of an epidemic occurring in the island of Thasus, off the coast of Thrace, described by Hippocrates, presenting many features of resemblance to relapsing fever "The chief points of resemblance between the ancient and modern epidemics are the invariable occurrence of relapses, the marked character of the crises, and the frequent associations with the more ordinary events of the disease of copious perspirations, hemorrhages particularly epistaxis, jaundice and splenic enlargements "[8]

From Carlisle's summary of the various reported epidemics and sporadic cases we learn that at one period relapsing fever was regarded as being indigenous to the British Isles J Warburton Begbie[8] gave as a synonym the term "epidemic fever of Scotland or Ireland "

4 Carlisle, R J Jour Infect Dis , 1906, iii, 233

5 Hirsch, A (see Carlisle) Handbook of Geographical and Histological Pathology, 1, London, 1883

6 Blanchard R Bull Acad Med , 1907, 5111 Abstr in Jour Trop Med and Hyg 1908, xi, 58

7 Hippocrates Epidemiorum Hippocratis, Liber Primus, Sectio Secunda, Status Tertius

8 Begbie J W Reynolds' System of Medicine, Lippincott, Philadelphia, edition 2, 1, 456

Relapsing fever has frequently been associated with typhus fever and with the insanitary conditions which favor the development of typhus fever It was recognized in Scotland and Ireland as early as 1817 and after several epidemics was last seen there in 1871 The cases in the United States reported by Austin Flint occurred in 1850-51 Clymer at Philadelphia in 1844 recognized it among Irish immigrants there It was at this time that relapsing fever was very prevalent in the British Islands, particularly at Edinburgh The disease in the United States did not spread very far A few cases occurred in Washington, Maryland, New Jersey and Connecticut One case was noted in Boston Flint's cases were observed in Buffalo, where he was practicing at that time Philadelphia and New York City were visited by an epidemic in 1869

There have been numerous epidemics in Europe, occurring in Russia for the first time in 1833 at Odessa, a seaport There have been epidemics in St Petersburg, Warsaw, Moscow, Novgorod and many other places in Russia The United States Consul-General's office reports the total number of deaths in Russia from relapsing fever in 1901 as given by the Medical Department to be 2 466 out of a total of over 700,000 deaths from infectious diseases

Many cases have been reported from India H Vandyke Carter[9] thought that relapsing fever was constantly present in Bombay

Germany has been visited by epidemics from time to time Obermeier[10] made his observations on relapsing fever during the epidemic of 1868-73 in Berlin Germany has been free from an epidemic since 1880 One imported case was discovered in Hamburg in the person of a Persian emigrant on his way to the United States In spite of the emigration from Russia at present and from Great Britain and Ireland in the past when epidemics of relapsing fever were present, it is to be noted that the disease has never gained a foothold in the United States Relapsing fever patients are infectious for a very long period, four to seven weeks throughout the entire course of the disease, giving a suctorial insect or acarid abundant opportunities to take on the spirochete so that its failure to spread when introduced is strongly indicative that the conditions are unsuitable for the continued existence of the intermediary or alternate hosts—insects, acarid or rat

The spread of relapsing fever during the past century may be related to the distribution of *Mus decumanus* over Europe and around the world

9 Carter H V   Spirillum Fever London 1882
10 Obermeier O   Centralbl f d med Wissensch, 1873 p 145

Fiom a study of the epidemiology of 1elapsing fever we would expect to find cases appear in seapoit towns and those in the inteiior reached by emigrants or sailois from places where 1elapsing fever was endemic

Thirty-one cases of 1elapsing fever have been recognized in the Commission hospitals in the canal zone during thiee yeais out of about 65,000 admissions, where blood examinations are made of every patient enteiing the medical wards The disease heie has not been confined to one race oi nationality

Table 1 records certain clinical data of interest in connection with seventeen cases occuriing during 1907

TABLE 1—CLINICAL DATA IN 17 CASES

Whites (15)			
Ameiicans	4	Gieek	1
Geimans	2	Tuik	1
Spaniaids	4	**Blacks (2)**	
Scotch	2	Maitiniquan	1
Italians	1	Antiguan	1

AGES		LENGTH OF RESIDENCE ON THE ISTHMUS (2 months to 3 yeais)	
13 yeais	1	2 months	1
21 yeais	1	3 months	4
22 years	1	4 months	1
26 yeais	1	4½ months	1
27 yeais	3	5 months	1
30 jears	2	6 months	1
32 yeais	2	6½ months	2
35 years	1	7 months	1
36 yeais	1	11 months	1
39 yeais	1	15 months	1
40 yeais	1	24 months	1
44 yeais	1	30 months	1
45 years	1	36 months	1

OCCUPATIONS		PLACE OF RESIDENCE ON THE ISTHMUS	
Laboiers	11	Colon and Ciistobal	5
Caipenteis	2	Rio Grande	1
Cable operatoi	1	Ancon diedge (suction)	1
Sailor (diedge)	1	Gatun	7
Engineei	1	Empiie	1
Unknown	1	Mindi	1
		Coiozal	1

It is to be noted in Table 1 that there is a dispioportionate number of cases among white employés—7 to 1—while the number of white to negro employés during the period from which the data was compiled was moie nearly 2 to 7 The average number of white employés for the yeai 1907 was 10,709, while the average numbei of black employés for the same period was 28,634 The seventeen cases tabulated were distributed among natives of nine countries, who had lived on the isthmus from two to thiity-six months, thirteen of the seventeen patients, in all probability, developed the disease on the Atlantic or Colon side of the isthmus, wheie theie appeai to be two foci of infection, Colon and Gatun, the formei a seapoit and the latter a village six miles fiom Colon on the Pan-

ama railroad, on the site of the proposed locks, where a large number of laborers are quartered

It is not intended to discuss, at any length, the clinical aspects of relapsing fever, but, more particularly, to give an account of some observations which it is hoped will throw some light on the nature of the micro-organism causing the fever found on the Isthmus of Panama

Attempts to identify the spirochete of relapsing fever by means of morphological and staining characters are subject to grave inaccuracies, for there is a fairly wide limit to the variations of length width, number of spirals, regularity of curvature and homogeneity in the same strain in different animals of the same species and at different periods during the infection

The terms "spirillum' and spirochete' are used at present indiscriminately when applied to the micro-organism causing relapsing fever With high magnification and better methods of staining and cultivation it may be possible to classify the spiral-shaped micro-organism in groups according to size, the number and arrangement of flagella, according to their shape—cylindrical or ribbon-shaped, according to their pathogenicity, according to their amenability to culture

Spirochetes are almost as widespread as bacteria In the blood stream they are associated with relapsing fever in men and the spirillosis of geese, goats, horses, rats, mice, fowl, sheep, cows and bats Spirochetes have been found in non-specific ulcers on the external genitalia ulcers on the legs or body tropical ulcers, in stomatitis and in intestinal inflammation and ulceration They have been found at autopsy here in Panama in most cases of gangrene of the lung and in other lesions of the respiratory tract In a case of sprue, recently, smears from a parchment-like membrane at the margin of the teeth showed a pure culture of spirochetes and fusiform bacilli Spirochetes are practically always found in inflammatory conditions of the mouth particularly of the gums It is not uncommon to find spirochetes associated with protozoa in infections of the intestinal tract of man and the lower animals

Insects harbor spirochetes, which have been found in their intestinal tract sexual organs and ova Several varieties of spirochetes are found in natural waters particularly in the surface pellicles of stagnant waters

Schaudinn[11] directed the attention of the medical world to a group of spiral-shaped micro-organisms more especially to one member of the group which he has designated *Treponema pallidum*, and with Hoff-

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11 Schaudinn F and Hoffmann E Gsndhtsamte 1905 xxii 527

mann, in 1905, has shown to be almost constantly present in the tissues of persons suffering from syphilis   The same year Castellani[12] described the spirochetes found in yaws

The spirochete of relapsing fever was discovered by Obermeier in 1873, who observed it for the first time in 1868 while studying an epidemic of relapsing fever in Berlin   Obermeier's observations were made with the spirochete of European relapsing fever, a disease belonging to the general class of relapsing fevers, but one which must be differentiated from the tick-fever of Africa and the fevers of Bombay and the Isthmus of Panama

It is impossible at the present time to differentiate the varieties of spirochetes of recurrent fever by cultural methods, and it can not be said that morphology affords an accurate means of distinguishing them, for in the observations on the isthmian relapsing fever the spirochete has exhibited considerable variation in size, length, number of spirals and in staining qualities   It will be necessary then to adopt as a means of differentiation the effects of the micro-organism on man and susceptible animals—animal reactions and the effect of the serums and cells of susceptible animals on the micro-organism—agglutination, lysis and phagocytosis

H Vandyke Carter published some notes in 1877 and a complete description in 1882 of the spirillum fever of Bombay   The disease appeared in Bombay in 1877, being introduced by immigrants from famine districts   Carter successfully inoculated monkeys with the spirochete of Bombay fever   Rogers'[13] description of the epidemic is very much like that of Welsh[14] of an early epidemic in Scotland, the disease spreading through families and attacking clinical clerks and hospital attendants   According to Norman Chevers and Carter, relapsing fever has always existed in India   During periods of famine the mortality has been very high   It is to be noted that vermin are particularly active in debilitated persons

Human tick-fever, or the relapsing fever of the Congo was first observed by Livingstone[16] in 1857   The etiologic factor, *Sp duttoni*,

12 Castellani, A   Jour Ceylon Brit Med Assn , 1905, ii, 54
13 Rogers, L   Fevers in the Tropics, London 1908, Oxford Med Publication Henry Frowde
14 Welsh, B   A practical treatise on the efficacy of blood-letting etc , Edinburgh, 1819
16 Livingstone   Missionary Travels and Researches John Murray London, 1857 Chapters xix pp 283 382 xx, pp 628 629

TABLE 2—SOME OF THE RELATIONSHIPS OF THE SPIROCHETES AND THE RESPECTIVE DISEASES CAUSED BY THEM

	Panama	Carlisle	Africa	Europe	Asia
Febrile paroxysms in man					
Number	3 4	3	5 6	2 3	2 3
Duration	2 days + —	2 days	1 day + —	3 9 days	?
Severity of disease	Mild	Mild	Severe	Severe	. Severe
Number of Spirochetes in blood during paroxysm	Very few, 1 to 30 fields + —	Very few, 2 to cover slip + —	2 to 3 per field	1 to field	?
The infection in monkeys	Mild with relapses	Mild with relapses	Severe and fatal, with relapse	Severe, with re lapses *	Very mild †
The infection in white mice	Mild, 2 relapses	?	Severe several paroxysms	Mild, naturally not susceptible	Mild, infected with difficulty
The infection in white rats	Mild, 1 paroxysm	Mild, 1 paroxysm	Severe, several paroxysms	Mild, naturally not susceptible	Mild, infected with difficulty

* Uhlenhuth and Handel
† Mackie

was discovered by Ross[17] and Milne in 1904 and by Dutton and Todd[18] in the same year

Dutton and Todd studied the disease in man and monkeys and produced the disease in monkeys by means of naturally infected ticks, *Ornithodoros moubata,* and in one experiment by means of young ticks, newly hatched in the laboratory, from eggs laid by infected parents

In America there have been several epidemics and occasionally sporadic cases In the earlier epidemics in the United States, the disease was introduced by Irish emigrants More recently sporadic cases have been reported in the United States among Russians, Armenians, or Spaniards The disease in most instances has been the European variety and is, undoubtedly, of this type in the two cases reported recently by Goldfarb[19] There is, however, a distinctly American type of the disease, such as the cases seen in Panama and the two cases studied by Carlisle

Fatal cases of relapsing fever were reported from Tuxpam, Mexico, during 1905 On the Isthmus of Panama, the disease was first observed and the diagnosis verified by blood examination at Colon Hospital in 1905, since when there have been recognized at Colon and Ancon hospitals 31 cases

Carlisle reported two cases of the American type in 1905 occurring at Bellevue Hospital, New York City The second case was derived from the first through the bite of an infected monkey The first was that of a ship steward who had recently visited Galveston and Key West

Among recent studies of relapsing fever are those of Breinl and Kinghorn[20] on *Sp duttoni,* Norris, Pappenheimer and Fleurnoy[21] and Carlisle, and Novy and Knapp's "Studies in *Spirillum Obermeieri*" Novy and Knapp fell into an error in calling the spirochete studied so thoroughly by them *Sp obermeieri* The clinical course of the disease in Carlisle's case and the animal reaction of the spirochete as determined by Norris and Novy are those of the relapsing fever of America, not that of Europe Mackie has recently reported an epidemic in India in which the body louse was thought to be the transmitting agent

17 Ross, P H , and Milne, A D   Brit Med Jour , 1904, ii, 1453

18 Dutton, J E , and Todd, J L   Memoir xiii, Liverpool School of Tropical Med   University Press of Liverpool

19 Goldfarb, S J   Med Rec , New York, 1908, lxxiii, 433

20 Breinl A , and Kinghorn, A   Memoir xi, Liverpool School of Tropical Medicine University Press of Liverpool

21 Norris, C Pappenheimer, A M , and Fleurnoy, T   Jour Infect Dis , 1906, iii, 266

The spirochetes of relapsing fever may be placed in four groups

Group A —The group causing a relapsing or recurring infection in man, monkeys, white mice and white rats, including *Sp duttoni* and the tick-fever of Africa

Group B —The group causing a recurring infection in man, monkeys and white mice, but with a single paroxysm in white rats   This group comprises the relapsing fever of Panama and the two cases studied by Carlisle

Group C —The group causing a recurring infection in man and monkeys but failing to cause an infection in small rodents with blood direct from human sources, yet causing an infection in small rodents after a preliminary passage through the monkey   This group includes the relapsing fever of Europe, caused by *Sp obermeieri*

Group D —The group causing a recurring infection in man and monkeys but only transient infections in white rats and white mice   This group includes the relapsing fever of Bombay caused by *Sp carteri*

Fig 1 —Course of case of relapsing fever of Africa   Note the remissions and intermissions during

These groups are also separated by differences in the clinical course of the respective fevers in man   The relapsing fever of Africa (Fig 1) is sharply differentiated from that of Asia, Europe and America by animal reactions specific agglutination, immunity and clinical features

The fever of Europe (Fig 2) is different from that of Asia and America in the duration of the febrile paroxysm which is longer in the European type than the others   and by animal reactions and other specific characters such as agglutination and immunity

The fever of Asia or Bombay differs from that of America chiefly in the animal reactions of the spirochete and the clinical features of the disease   the Asiatic fever being more fatal

Furthermore, as has been determined in this investigation, there is an individuality to the strains of spirochetes of the same species in the same locality, for an animal immunized to one strain is not immune to another strain from a different human source [22]

In this investigation of the relapsing fever of Panama the animal reactions of white mice, white and wild rats and monkeys have been worked out Experiments in immunity have been carried out, parallel infections with *Trypanosoma lewisi* have been studied, and the part played by the liver in the infection has been inquired into The specific nature of stains has been investigated, and the effect of certain anilin dyes in lowering the resistance of inoculated animals to the infection has been noted

the paroxysm and the subnormal oscillations of temperature during the afebrile period

SOURCE OF THE SPIROCHETES USED IN THIS WORK

Animals have been inoculated from four patients, but only two of the strains so derived have been carried on for any length of time The two strains used in this investigation will be designated as A and B

ORIGIN OF STRAIN A

Patient—L G , hospital No 33,107, from whom this strain was obtained, was a laborer, native of Spain, aged 39, length of residence on the Isthmus, three years residence Gatun, a village in the Canal Zone, six miles from Colon, and one of the foci of infection (See Fig 3)

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22 I have since learned that Carl Frankel (abstr in Jour. Trop Med and Hyg , 1908, xi, 70, from Klin Med , 1907, p 928) has made a similar observation with regard to the spirochetes of the African fever

Previous History —The patient was twice in hospital, two weeks in Colon hospital and two weeks in Ancon hospital   He had not taken quinin

Present Illness —He has been ill four days   Onset with chill followed by fever, since when he has had several chills and much fever

Clinical Notes (By D Summersgill) —The spleen was enlarged and tender, lungs, glands, liver, skin, blood vessels, nervous system, urine and stool negative   The blood contained a few spirochetes   Blood was taken for animal inoculation Oct 11, 1907, at 3 30 p m, when the temperature was 102 F   Spirochetes were present in the peripheral blood at this time   Four cubic centimeters of blood from vein at elbow were inoculated intraperitoneally into a small monkey *cebus* and 2 c c intraperitoneally in two white rats and two white mice

ORIGIN OF STRAIN B

Patient —B J (See Fig 4), from whom this strain was obtained, was a patient in Colon hospital, laborer, native of Turkey, age 27, residence, Gatun, length of residence on the Isthmus, six and one half months

Previous History —The patient had been in hospital once, had had malaria many times, no dysentery

Present Illness —He had been sick three months, had swelling of feet with ulceration, and weakness

Physical Examination (By Di Brem) —Abdomen pendulous   Movable flatness in flank—indistinct fluid   Mucosæ pale   Liver enlarged   Skin waxy Tongue pale, flabby and coated   Lungs and glands negative   Spleen palpable 9 cm below costal margin   Blood vessels soft •Pulse full   Heart   Presystolic murmur prolonged into systole, blowing and coarse, heard all over precordium with maximum intensity at apex, pause in aortic and pulmonary area, transmitted into vessels of neck, to axilla and towards sternum along costal margin Feb 5, 1908   Apex beat not visible   Palpable in the fourth and third interspaces, 12 cm to the left of the sternum   Soft bruit accompanying the first sound all over precordium   Best at apex   Blood pressure 116

Leucocytes, Jan 21, 1908, 4,500, Jan 22, 1908, 6,000

Red blood cells, Feb 3, 1908, 4,800,000, red blood cells, Jan 8, 1908, 3,344,000

Hemoglobin Jan 15, 1908, 70 to 75 per cent , Jan 16, 1908, 55 per cent , Feb 2, 1908, 69 per cent

Urine and stools, negative

Blood taken from patient's arm Jan 21, 1908, and inoculated into two white rats intraperitoneally

CHARACTERISTICS OF THE MICRO-ORGANISM

In human blood, in the relapsing fever of Panama, there are comparatively very few spirochetes seen during the paroxysm, one to forty or fifty fields or perhaps only three or four to a cover-slip   In the period between paroxysms it is rarely possible to find a spirochete in the peripheral blood   In none of the cases studied here has the spirochete been present in what might be called considerable numbers   This observation is another means of differentiating the fever of Panama from that of Europe   Blood films taken from cases of the relapsing fever of Europe often show considerable numbers of spirochetes   Films from a case of European relapsing fever (Fig 2), which I have studied through the kindness of Di Samuel J Goldfarb, often show six spirochetes to

one oil immersion field   Such a picture is never seen in blood films from cases of the fever met with here

The description of the spirochetes is based on observations made with richly infected blood of white mice and white rats

MORPHOLOGY

The movements of the spirochete are very rapid, except just before its disappearance from the blood stream   At this time observations of the nature and character of the movements may be made, or the motions may be slowed down by treating a drop of blood with two or three drops of citrated saline solution and making a cover-slip preparation   At first the motion of the spirochete is violent, in two or three hours it can be made out with great ease   Red blood corpuscles become segregated and in the clear spaces spirochetes will have gathered and can be seen moving
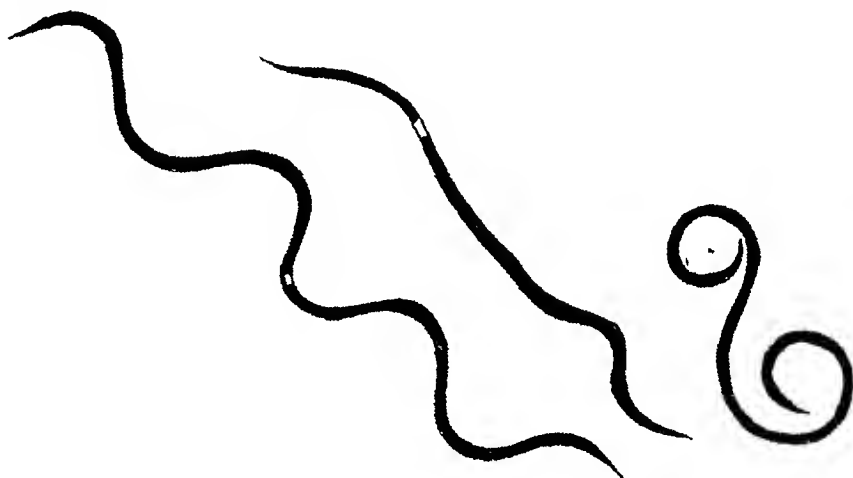
Fig 5 —Spirochetes from blood of Rat 31, seen at height of the infection showing one normal double form A   one stretched out form B, and one recurved form C, in one cover slip preparation

in various directions   Frequently a spirochete may be seen to be attached to a red blood corpuscle by an invisible flagellum, the margin of the red blood corpuscle then becomes pulled out and the whole cell distorted even dragged away down-stream with a spirochete evidently attached, yet always keeping nearly a red cell's diameter away   When the red cell is fixed, the attached spirochete may be seen to rotate to the right, apparently trying to go forward, then after a pause the rotatory movement is apparently reversed, this reversed movement frequently carries the spirochete away from the red blood corpuscle a short distance, though it still remains attached to it   During the pause in the rotation there is an opportunity to observe its outline and to determine whether the spirochete

is a spiral cylinder or ribbon This question is difficult to determine
when the spirochete is met in cross-section During the pause just men-
tioned some spirochetes appeared to be spiral ribbons One appeared to
be curved in one plane only—on the flat In fresh citrated blood prepa-
rations the observations were made with artificial light, Zeiss 2 and 3
mm objectives and 6 8, 12 and 18 oculars Under these conditions,
while the various motions of the spirochetes were made out with ease,
the impression received as to the topography of the spirochete was prob-
ably illusory Any one who has watched the polished balls on the gov-
ernor of a stationary engine, when illuminated by artificial light, knows
how by a slight effort of the will the balls may be seen to rotate to the
right or to the left, just so with the spirochetes One is not absolutely
sure that it is rotating to the right or to the left, but one feels sure that
it is rotating Perhaps the physicists may throw some light on this mat-
ter by telling us what the optical effect on the observer will be under, say,
two hypothetical conditions light from an incandescent lamp reflected
by a mirror through substage condenser, glass slide, blood serum, through
the transparent body of a spirochete having a refractive index of $1 + x$
and a diameter of 0 3 micron under the following conditions   (a) the
body of the spirochete rotating in a plane transverse to the rays of light,
the body being a spiral ribbon, (b) the body being a spiral cylinder   I
believe the question involved insoluble by a mere inspection of fresh or
stained specimens

At the end of three hours in citrated preparations the spirochetes
frequently appeared attached to a red blood corpuscle at one end The
movements of the attached spirochete cause the red blood corpuscle to
change its outline to a very marked degree, frequently pulling it out
into a pear-shaped body The spirals or curves of the spirochete push
and pull the red blood corpuscles out of contour, giving one the impres
sion that the spirochete is possessed of great rigidity

Besides the rotary movement, there is an undulating movement or
tremor , the spirochete does not always move rapidly away from the field,
but rather rotates and trembles in one spot and then darts off a short
distance within the field

In citrated blood preparations, at the height of an infection many
spirochetes may be seen in a prefragmenting stage their motion is slow
and there is a tendency to wreath or ring formation, then two extremi-
ties becoming attached and they may be seen to shake and tremble the
body of the spirochete apparently breaking up, while the fragments are
apparently held in apposition by a sheath or envelope The effect is very
much like that of an agitated chain

In ciliated blood preparations, the spirochetes, after a short time, are commonly found in the clear spaces formed by the segregation of the red blood corpuscles

The undiluted fresh blood preparation at room temperature, 76 to 82 F, presented on one occasion, at the end of sixteen hours, about the same picture that the ciliated blood did at the end of four hours

Aerotactism, such as is observed in fresh water flagellates, was never noticed   Aerotactism refers to the air-hunger observed in water flagellates from surface pellicles when studied in cover-slip films   These protozoa may be found in large numbers close to the margin of air bubbles

Agglutination is seen in fresh preparations at the height of an infection, the parasites may adhere to one another end to end or side by side, the bodies of the spirochetes are probably fastened by entangled flagella

When fresh and stained preparations are made from the same drop of blood, the fresh specimen frequently shows all regular forms, while
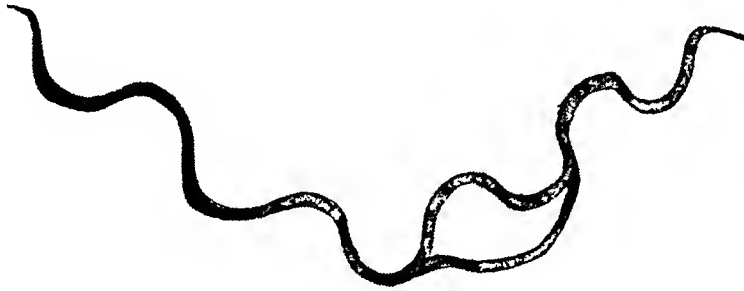
Fig 6 —Blood from Mouse 8   The clear space in the middle is suggestive of transverse fission and the loop is suggestive of longitudinal fission

the stained specimen may contain many bodies curved or straightened out   Drying and staining processes, therefore, may alter the regularity of contour of the spirochetes

In stained preparations, the length, contour, number of spirals, the presence of flagella and staining qualities of the spirochetes were noted   Great variation in the regularity and number of curves was noted   In one film coarsely and finely curved forms were seen, as well as coarse and fine curves in one organism   Irregular curvatures, straightened and recurved forms were frequently encountered

Toward the end of an infection achromatic spaces in the spirochete, or the prefragmenting phase, were frequently seen, sometimes as many as four spaces could be counted in one spirochete the length of which was 8 or 10 microns   These achromatic spaces are not to be confounded with the achromatic space which is present in the double forms, which

appears just before transverse fission and is always centrally located and wider than the former

The act of subdivision was not observed The centrally located achromatic space in the double form is strongly suggestive of transverse fission, while a very few loop forms with an apparent longitudinal split were suggestive of longitudinal fission The achromatic zones are well demonstrated in films stained with acetone gentian violet In these preparations, curiously, there is never the least semblance of a periplast, while in the films stained with some modification of the Romanowsky stain a faint line, bridging over the achromatic zone, is noted Some films which were stained with Muir's flagellum stain showed spirochetes with a single, terminal, faintly staining flagellum, its diameter decreasing toward its free extremity Occasionally, in a film stained with acetone gentian violet, a ring form could be seen In these instances, in which the free extremity of a flagellum was in relation with the opposite end of the spirochete, a little more than one-third

Fig 7 —Spirochete from blood of Rat 66, showing large and small curves in one individual

of the circumference of the ring would be more faintly stained than the rest and tapering, corresponding to a flagellum In several of the acetone gentian violet preparations the appearance of spiral ribbons seemed unmistakable In double infections of spirochetes and trypanosomes films were stained in various ways, yet, whenever the chromatin filament of the trypanosome was in evidence, nothing at all like this structure could be made out in the spirochetes A priori, why should the spirochete of relapsing fever be provided with a chromatin filament? The spirochete is a rigid spiral staining homogeneously, in every way like a bacterium, never like a protozoon Its peculiar motion is probably due to rotation caused by a lashing contracting movement of the flagellum inducing a rotation of the body of the spirochete, the rotation being favored by its flat or ribbon-shaped contour Its body is rigid and not flexuous to the degree observed in trypanosomes The spirochete stains homogeneously except just before its disappearance from the peripheral blood, when achromatic spaces or zones appear—the presegmenting

phase It is stained purple with polychrome blues as bacilli are Blue vacuolated cytoplasm with chromatin granules, such as one sees in protozoa, is never noticed, and it is decolorized by Gram's method A very striking characteristic of spirochetes stained by gentian violet is the decolorization of the spirochete, either at once or after a few days, on exposure to diffuse sunlight Films from Rat 31 colored with acetone gentian violet stained intensely and showed the achromatic zones beautifully A few days later the spirochetes were completely decolorized and could be made out only by their sinuous transparent bodies, the red blood corpuscles and leucocytes, however, retained the gentian violet perfectly A similar result was observed whenever a film was stained with Muir's too old flagellum stain, even when it had been previously stained with a polychrome blue stain

SIZE

Measurements of length were made from stained preparations of the blood of rats and mice Single spirochetes in which no achromatic zone could be detected measured from 7 2 to 13 2 microns Double spirochetes having a central achromatic zone measured from 13 2 to 17 microns The number of complete S-forms in single spirochetes having no achromatic zone varied considerably in the same film The above measurements were made from spirochetes seen in the blood of Mouse 1, at the first remove from man

ANIMAL REACTIONS

In man the disease is characterized by recurring paroxysms of fever lasting, usually, from twenty-four to forty-eight hours The temperature rises slowly or rapidly to 103 or 104 F, occasionally to 105 F There is always a chill and the access can not be distinguished by inspection from a malarial paroxysm The duration of the first paroxysm is not definitely known, but is probably three days The temperature falls slowly or suddenly to normal with the subsidence of symptoms, when, after a period of from three to eight days, oftenest five or six days, there is another paroxysm resembling the first and lasting about the same length of time The usual number of paroxysms is three There may be abortive paroxysms in which the temperature rises a degree or two above normal for two or three hours During the febrile paroxysms a a few spirochetes appear in the peripheral blood Very rarely a spirochete may be detected during the afebrile period The spleen is always enlarged and tender, the tongue, pale and coated Epistaxis occurs occasionally during febrile paroxysm (during the first relapse in case of F S) The pulse and respirations are accelerated during the febrile

paroxysm Ten or twelve hours after the drop in temperature there is profuse sweating Several cases were complicated by diarrhea and colitis with pus and blood in the stools There have been no deaths in uncomplicated cases

ANIMAL REACTIONS WHITE MICE

Among animals the white mouse is the most susceptible Mouse 3 was infected with blood containing not more than one or two spirochetes As it was found that a drop or two of infected mouse-blood was sufficient to infect another mouse, and as it was desired to observe the progress of the disease without unnecessary sacrifice of the limited number of animals at my disposal, blood from the tail of an infected mouse was expressed into a Petri dish containing citrated saline solution to prevent clotting, this was injected into the peritoneal cavity of the next mouse in the series Fifteen mice were infected in this way

The disease in white mice is very much like that in man There were three paroxysms, during which spirochetes appeared in the peripheral blood The temperature of the smaller animals was not taken on account of the wide normal daily variation and the influence of various undetermined factors in causing irregularities in the temperature curve and making its record valueless The temperature of the larger animals—goats, monkeys and dogs—was found to vary similarly

The number of paroxysms, number of spirochetes in the blood and the period of incubation depend on a number of factors The period of incubation by the method of inoculation used varied from twenty-four hours to six days Mouse 3 inoculated from Mouse 1 with five drops of tail blood containing one spirochete to 500 fields, showed one spirochete in 100 fields after a period of twenty-four hours Mouse 13 was inoculated from Mouse 12, when the blood from No 12 showed no spirochetes in 500 fields The period of incubation in No 13 was five days and the infection was a typical one with three paroxysms

Mouse 1 was inoculated directly from the patient during his second paroxysm No spirochetes were seen until the third day, when there were two to a field Two c c of uncitrated blood were used to infect Mouse 1 The infection was un usual, inasmuch as the period of incubation, in spite of the large amount of blood used was prolonged, yet the spirochetes remained constantly in the animal's blood without intermission, for ten days, when death occurred Continuous infections have been observed in two animals, a white mouse and a black rat The issue was fatal in each case During the course of the infection in Mouse 1 there was a high degree of polychromatophilia, basophilic granular degeneration of the red blood cells leucocytosis and a marked diminution in the number of red blood cells Dyspnea and convulsions occurred before death At autopsy the spleen was greatly enlarged and there were two encysted larval tapeworms (*I echinococcus murinum*) in the liver The day before death spirochetes were rapidly increasing in the peripheral blood there being 10 per field, with consider able agglutination The mouse therefore, died at the end of a paroxysm (See chart of Mouse 1 Fig 8)

Mouse 2, inoculated intraperitoneally with 2 c c uncitrated blood directly from patient, had five and possibly six paroxysms with recovery There was a marked remission during the first paroxysm, and as the blood was not examined on October 15 it is not known whether spirochetes were absent on that day or not (See chart of Mouse 2, Fig 8)

Mouse 3, inoculated from Mouse 1, had a period of incubation of twenty-four hours and four paroxysms

Mouse 4, inoculated from Mouse 2, had a period of incubation of forty eight hours, only two paroxysms, and died six days after the disappearance of spirochetes from the peripheral blood At autopsy the spleen was not much enlarged, and spirochetes were absent from the peripheral blood During the progress of the infection there was much polychromatophilia and basophilic granular degeneration of the red blood cells This basophilic granular degeneration has probably been mistaken for the resting forms of spirochetes (See chart of Mouse 4, Fig 8)

Mouse 6, inoculated from Mouse 1, had three paroxysms and died three days after the disappearance of spirochetes from the peripheral blood (See chart of Mouse 6, Fig 8

Mouse 9, inoculated from Mouse 3, had a period of incubation of 48 hours, two paroxysms, and was accidentally killed thirteen days after second and last paroxysm, during which period paroxysms were absent from the peripheral blood (See chart of Mouse 9, Fig 8)

Mouse 12, inoculated from Mouse 6, had a period of incubation of forty-eight hours and three paroxysms, while spirochetes remained absent thirteen days after the last paroxysm (See chart of Mouse 12, Fig 8)

The amount of blood used to inoculate these animals was about five drops This was caught in a sterile Petri dish containing 5 c c of sterile, citrated, normal saline solution, and injected immediately intraperitoneally

The spirochete counts were made from smears on cover-slips stained with Leishman's or Hasting's stain A field was that which was obtained by a Zeiss 2 mm objective and No 6 ocular When spirochetes were sparse at least 300 fields were counted, frequently 500 or a thousand, sometimes, three or four films

It will be noted that in the initial paroxysm there is a greater number of spirochetes per field per day and the duration of the paroxysm is somewhat longer than the subsequent ones The first paroxysm lasts about three days The period between the first and second paroxysm is from four to five days The second paroxysm lasts from two to three days, this may be followed by an intermission of four or five days, and followed by a third relapse lasting one, two or three days

In severe infections the period of intermission between relapses may be shortened to one day During the relapses the mice are slightly indisposed and take little food After taking the blood films or removing blood for inoculation the tails of some infected mice bled profusely and required an application of collodion

Mouse 1 lost considerable blood, which probably helped to cause some of the blood changes noted above and may have influenced the character of the infection and the fatal issue
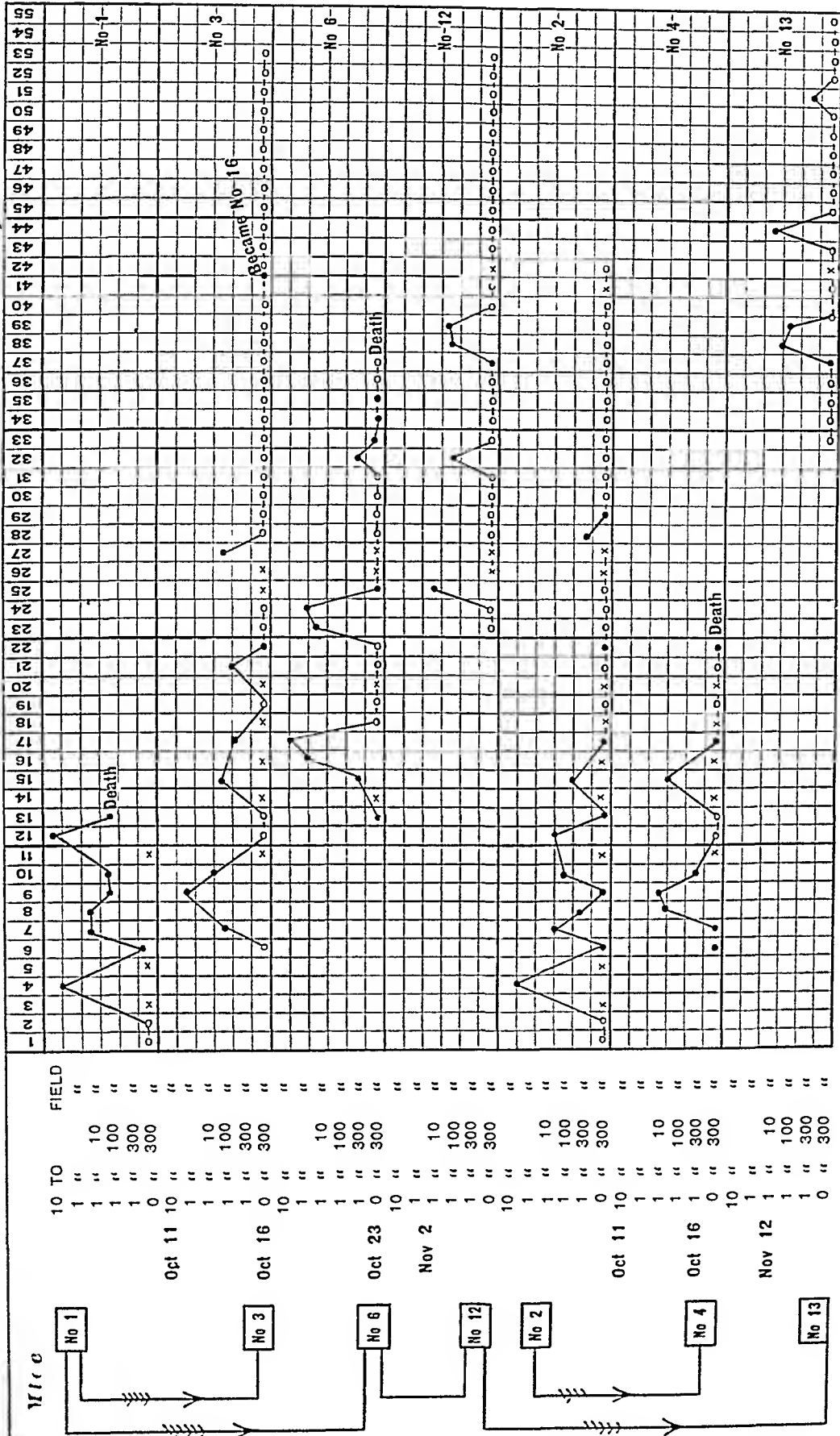
Fig 8—Chart of group paroxysms in white mice, showing the numbers of spirochetes in the peripheral blood Circles (O) signify no spirochetes in 300 or more fields, crosses (X) blood not examined on this day

Of the deaths in mice all but two occurred several days after spirochetes had disappeared from the peripheral blood   One of these had, in addition to the heaviest infection noticed in mice, a profound anemia Most of the dead mice had encysted larval tapeworms (*Echinococcus murinum*) in the liver

An attempt was made to ascertain if there was a definite or constant periodicity in the relapses which might be correlated with a life cycle of the parasite, the period of which might be suggested if the paroxysms appeared on similar days in the original animals and in those subinoculated from them, there was, however, no conformity between such paroxysms   (See Fig 8, chart of group paroxysms)

ANIMAL REACTIONS, WHITE RATS

The infection in white rats is characterized by a single paroxysm lasting two or three days followed by the rapid disappearance of spirochetes from the blood stream   The disappearance is not complete, as will be shown later, but it is rarely possible to demonstrate spirochetes in the peripheral blood twenty-four hours after the height of the infection

The period of incubation in white rats depends on the number of spirochetes injected, among other factors   When minimal amounts of tail blood are injected the period of incubation is from two to five days When larger amounts of heart's blood are used spirochetes may be demonstrated sixteen to eighteen hours afterward

Peripheral (tail) blood uniformly requires a longer period than heart's blood to produce an infection, and it may be possible that bodies antagonistic to the multiplication of the spirochetes are present in larger quantities in peripheral blood than in heart's blood

Several rats were examined during periods of 14, 15 and 16 days after the paroxysm for the presence of spirochetes, but none were ever demonstrated, save in one case—Rat 37—when one atypical, straightened-out, swollen form was seen on the third day after the height of the infection

When minimal amounts of infected peripheral blood were injected spirochetes would appear, usually after two or three days, in small numbers—viz   one spirochete to from 13 to 500 fields   On the following day one spirochete to two fields might be counted, after which they would immediately disappear

TABLE 3 —COURSE OF INFECTION IN RAT 22

Inoculated Dec 4, 1907, a m from the tail blood of Mouse No 17, when this blood contained one spirochete to 100 fields about 15 drops of blood being used

12/ 5—0 spirochetes in 300 fields	12/11—0 spirochetes in 300 fields
12/ 6—0 spirochetes in 300 fields	12/12—0 spirochetes in 300 fields
12/ 7—1 spirochete in 300 fields	12/13—0 spirochetes in 300 fields
12/ 8—1 spirochete in 2 fields	12/14—0 spirochetes in 300 fields
12/ 9—0 spirochetes in 300 fields	12/15—0 spirochetes in 300 fields
12/10—0 spirochetes in 300 fields	

The injection of larger quantities of heart s blood, or more severely infected blood from rats, was followed by the appearance of one spiro chete to 25 or 100 fields within twenty-four hours, and after forty-eight hours from 25 to 100 spirochetes in 100 fields   At the end of seventy-two hours there was either complete disappearance or the presence of spirochetes in numbers of from 1 to 7 or more per field   On the fourth day, or at the end of ninety-six hours, it was extremely rare to find spirochetes in the peripheral blood   Rat 20 had one spirochete per 100 fields on the fourth day of the infection   Ordinarily the paroxysm lasted three days   (See Table 4, showing course of infection in Rat 20)

The duration of the paroxysm and the number of spirochetes appearing in the peripheral blood of the inoculated rat do not depend entirely on the number of spirochetes injected, as the following experiment shows

TABLE 4 —COURSE OF INFECTION IN RATS 19 AND 20

Inoculated 11/26/07 from heart s blood of Rat 18   Rat 18 had one spirochete to 500 fields when examined in the a m   When examined six hours later at time of death and subinoculation of Rats 19 and 20, there were two spirochetes to 100 fields in heart's blood

Amount inoculated 0 3 c c	Amount inoculated, one third as much as Rat No 19, for 0 1 c c
11/27—1 spirochete to 50 fields	11/27—1 spirochete to 33 fields
11/28—1 spirochete to 25 fields	11/28—1 spirochete to 6 fields
11/29—2 spirochetes to 1 field	11/29—1 spirochete to 1 field
11/30—0 spirochetes to 300 fields	11/30—1 spirochete to 100 fields
12/ 1—0 spirochetes to 300 fields	12/ 1—0 spirochetes to 300 fields
Fourteen daily successive examinations were made without finding spirochetes	Fourteen daily successive examinations were made without finding spirochetes

In this experiment Rat 20 receiving at time of inoculation one-third as much infected blood as Rat 19, had a slightly severer infection and a longer paroxysm

White rats may appear very slightly indisposed for half a day during the paroxysm   Only one death occurred this was after the disappearance of spirochetes from the peripheral blood and was due to pneumonia

White rats were infected directly from two different human sources and in both instances the period of incubation was forty-eight hours although large amounts of blood were used—2 c c and 5 c e of undiluted blood

It is to be noted that during the course of the infection there are from thirty to fifty times as many spirochetes in rat s blood as in man s blood

ANIMAL REACTIONS   WILD RATS

The gray rat (*Mus decumanus*), when kept in small cages for convenience in handling, does not survive captivity and the rather rough handling necessary in making inoculations   Most of the rats of this variety brought to the laboratory and confined in small cages died within a few days, consequently they were not suited for a study of this infection

The black rat (*Mus rattus*) may be kept for weeks and months in small cages   Several black rats have been inoculated, and, as these rats were harboring *Trypanosoma lewisi*, an opportunity was offered for studying the parallel infection of trypanosomes and spirochetes

Wild Rat 5 was inoculated intraperitoneally with one drop of blood from Mouse 5 and died on the third day   Spirochetes were not found at any time during the three days

Wild Rat 25 was inoculated from Rat 24 when the latter had 8 spirochetes per 100 fields using citrated heart s blood   This rat had a mild continuous in
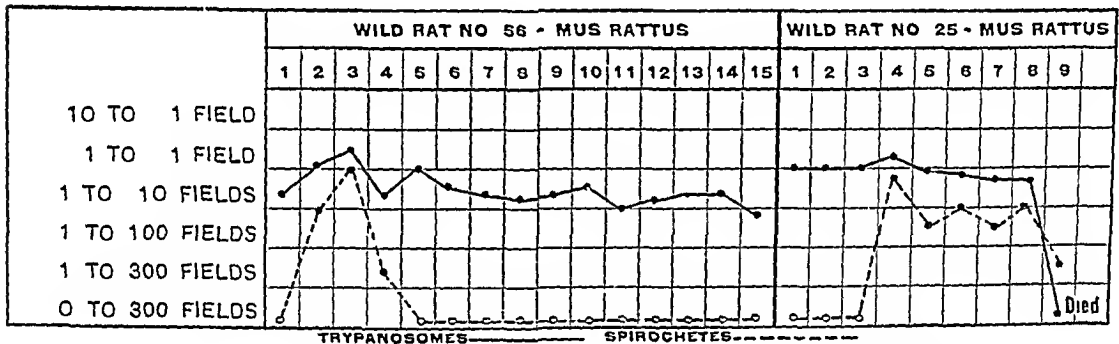
Fig 9 —Parallel infection of spirochete and trypanosomes

fection lasting six days, after an incubation period of seventy-two hours   Death occurred at the end of the sixth day   This observation may have some importance on account of the possibility of a suctorial intermediary host conveying the spirochete from a rodent having a slight continuous infection to man

Wild Rat 56 was inoculated from Rat 51 when the latter had 250 spirochetes to 100 fields, using citrated heart's blood injected subcutaneously at the base of the tail   This rat had an infection lasting three days after an incubation period of twenty-four hours

ANIMAL REACTIONS   MONKEYS

The infection in monkeys of the old world, genus *Macacus*, is similar to that in man and white mice, inasmuch as there is more than one paroxysm

Macacus 65 was inoculated on February 4 from Rat 63 when No 63 had 219 spirochetes to 100 fields   using citrated heart s blood   One c c of blood was inoculated intraperitoneally   Spirochetes appeared after twenty-four hours and remained in the peripheral blood three days, disappearing for five days and then reappearing for three days in about the same numbers as in the first paroxysm   There was a slight diarrhea noticed after the second paroxysm   During each

paroxysm there was some bleeding from the gums near two carious, upper, middle incisors   This blood from the gums contained spirochetes   The animal did not appear sick at any time during the course of the disease

The blood changes were slight polychromatophilia of red blood cells with some fine and coarse basophilic granular degeneration   These were noticed after the first paroxysm

At the beginning of the second paroxysm there was a slight drop in the temperature followed by a rise of 4 degrees above normal or to 106 4 F   The temperature was only slightly altered during the first paroxysm and was not greater than the variations noted during health   (See Fig 10)

ANIMAL REACTIONS   VARIOUS

A turtle, pigeon, frog and guinea-pig resisted an infection by infected rat's blood, which would have been sufficient to produce the disease in white rats   Two dogs and a goat were inoculated from human sources with blood obtained during paroxysms, but no infection resulted   It might have been possible to infect these animals if larger amounts of
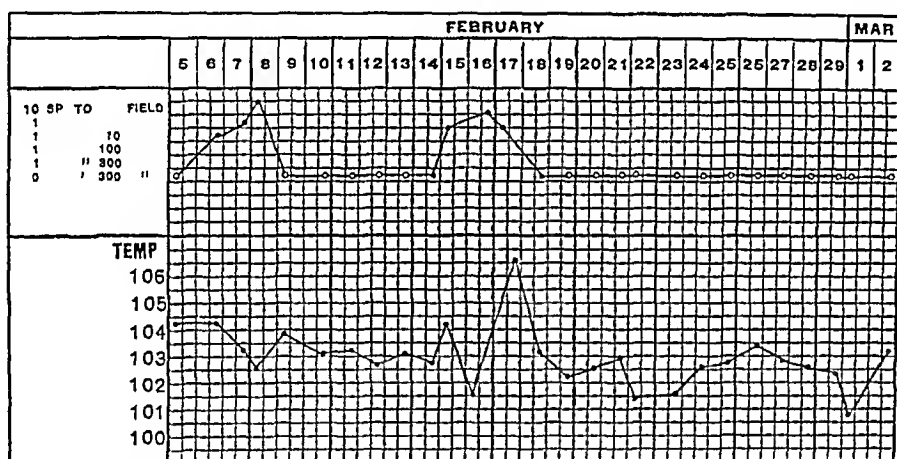
Fig 10 —The spirochetal and temperature curve in Macacus 65   Note that there were only two paroxysms and that the temperature was not disturbed during the first one

severely infected rat's blood could have been used, but the number of white rats at my disposal was so small that the greatest economy had to be exercised in subinoculations

A raccoon has also resisted infection

Novy and Knapp have shown that in the reactions of spirochetes and their hosts certain substances are produced which help to cause the disappearance of the spirochete from the blood and establish a qualified immunity against subsequent infections

At the height of an infection it is evident that some change is taking place in the spirochete   Stretched out and irregularly curved forms are seen, many of these have achromatic zones   The movement of the

spirochete is less rapid, prefragmentation and chain formation are noticed and agglutination always occurs   Agglutinins and lysins are undoubtedly formed, but there is not a complete dissolution of the spirochete at this time   The sheath or periplast always appears to be intact in organisms seen in the blood stream   It is the internal substance of the spirochete that become fragmented (Fig 11)   Besides this, the spirochete apparently is not completely broken up in the peripheral blood stream, for fragments are never seen there, either free or in any type of leucocyte If, however, as was observed by Levaditi and Manouélian,[23] with the spirochete of tick-fever, we sacrifice an animal at the height of an infection or a day or two later, it is possible, by Levaditi's silver impregnation methods, to demonstrate that the disappearance of the spirochetes from the blood stream has been due to the fact that
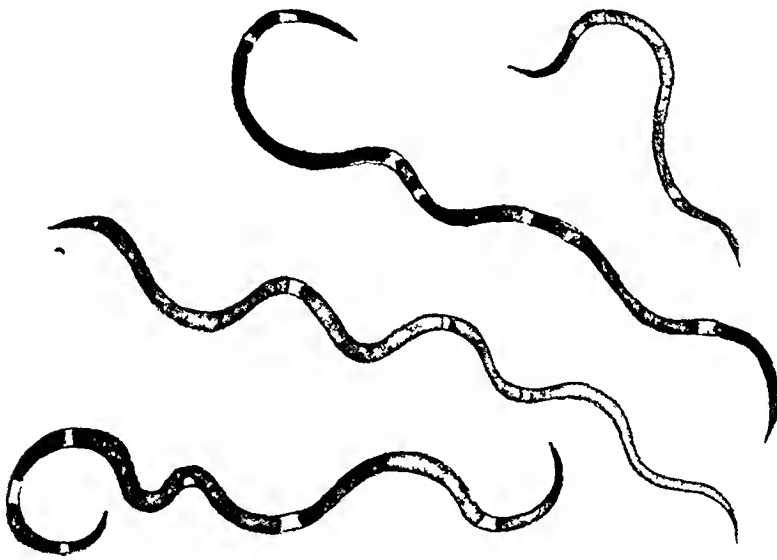
Fig 11 —Spirochetes from blood of Rat 31 seen at height of infection, showing fragmentation of the protoplasmic substance, and an intact sheath or periplast

they have been engulfed by endothelial cells lining the liver capillaries Throughout the liver large, swollen endothelial cells may be seen, their cytoplasm dotted with spirochetes in all stages of fragmentation From the appearance of the spirochetes within the endothelial cells it is probable that they are engulfed whole and that separation of the fragment occurs in the phagocytic cells by a solution of the periplasts

23 Levaditi and Manouélian   Ann de l Inst Pasteur 1907 XXI 295 Uhlenhuth and Haendel   Arb a d k Gsndhtsamte, 1907 XXVI, H 1 1   Manteufel Arb a d k Gsndhtsamte XXVII H 2, 327   Schellack C   Arb a d k Gsndhtsamte XXVII, H 2 364

The spirochetes disappear very rapidly from the peripheral blood after the height of the infection, but the disappearance is not complete for on three occasions it has been possible to infect rats when no spirochetes could be demonstrated in films of the infective blood In these instances the blood used was taken about twenty-four hours after the apparent disappearance of parasites from the peripheral circulation
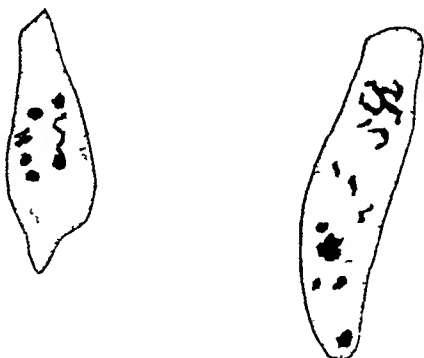
Fig 12—Endothelial cells from capillaries of the liver showing phagocyted spirochetes from Rat 26 killed at height of infection which had lasted three days Levaditi pyridin preparation
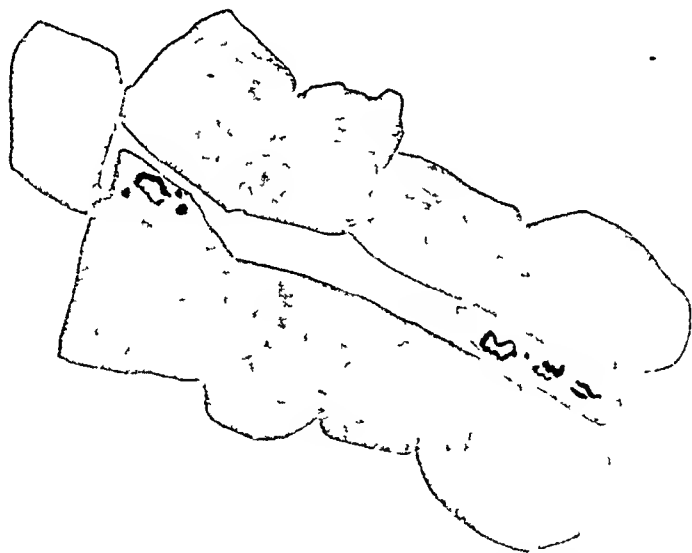
Fig 13—Section of liver of Rat 26 showing two endothelial cells of a capillary, containing phagocyted spirochetes   Levaditi pyridin preparation

The following experiments illustrate this point

Rat 57 was inoculated from Rat 55 when the latter had no spirochetes in 500 fields   Spirochetes appeared in the blood of No 57 four days after inoculation

Rat 47 was sacrificed when spirochetes had disappeared from the peripheral blood which was injected into Rat 48 spirochetes appearing in the blood of Rat 48 on the sixth day, at the same time another rat 49 was inoculated with an

emulsion of a portion of No 47's liver in citrated saline solution, spirochetes appeared in No 49 s blood after an incubative period of four days, or two days less than in No 48

In this last experiment it is to be noted that the liver emulsion, although containing but traces of blood, the animal having been previously bled to furnish heart's blood for the inoculation of Rat 48, was more infectious than heart's blood from the same animal

This experiment is interesting in view of the phagocytosis of spirochetes by liver endothelial cells These experiments, besides showing the infectiousness of decline blood or of postdecline blood, show that phagocytosis plays an important part in the bodily defence

If suitable emulsions containing liver endothelial cells can be prepared it might be possible to demonstrate the production of specific opsonins during the infection

IMMUNITY

During the course of the infection in white mice, white rats and wild rats a protective mechanism is developed which brings the infection to a close and confers a qualified immunity against a subsequent attack The protective mechanism is one largely of phagocytosis, aided, as shown by Novy and Knapp, by specific agglutinins and lysins The actively acquired immunity in white rats has lasted as long as forty-one days in individuals of the same strain White mice have remained immune to the same strain sixty days, in fact, all attempts to reinfect animals with the same strain as that from which they were infected have failed, as the following experiments illustrate

Active Immunity Mice

Mouse 16 (inoculated December 20 from Mouse 14 with blood containing 1 spirochete to 38 fields) was formerly Mouse 3, spirochetes had been last seen in the blood November 7 or thirteen days previously The immunity was sufficient to protect, spirochetes not being found in the blood during thirteen daily examinations

Mouse 61 (inoculated January 28 from Rat 59 when No 59 had 18 spirochetes to 10 fields, using citrated saline heart's blood intraperitoneally) was formerly Mouse 13 having had spirochetes in its blood for the last time on November 30 The immunity was complete as No 61's blood failed to show any spirochetes during subsequent daily examinations continued for nine days

Active Immunity Rats

Rat 43 (inoculated December 24 from Rat 38, when No 38 had 420 spiro chetes to 100 fields, using citrated heart's blood intraperitoneally followed by 10 drops saline solution of oreem) was formerly Rat 27, having had spirochetes in his blood for the last time December 16 The immunity was complete spirochetes failing to appear in No 43 s blood during the nine days subsequent to the last inoculation

Rat 58 (inoculated January 25 from Rat 57 which had 3 spirochetes to 100 fields using citrated saline heart's blood intraperitoneally) was formerly Rat 45

having had spirochetes in his blood from December 29 to 31 inclusive The immunity was complete, spirochetes failing to appear during thirteen days

Rat 60 (inoculated January 28 from Rat 59 when No 59 had 18 spirochetes to 10 fields, using citrated heart's blood intraperitoneally) was formerly Rat 33, having had spirochetes in his blood from December 16 to 18 inclusive The immunity was complete, spirochetes failing to appear during ten days

SPECIFIC CHARACTER OF STRAINS

The immunity conferred by one strain of spirochetes is not sufficient to protect against a second strain of the same species having a different origin For example, I found that, while it was impossible to reinfect white mice or white rats with strain A, the one used to infect them originally, it was possible to infect them by using strain B The history of these two strains has been given above Strain A was obtained from Case 3 Oct 11, 1907, during the antepenultimate paroxysm, passed through 16 white mice and about 50 white rats Strain B was obtained more recently from a case occurring in Colon Hospital Blood was drawn during the penultimate paroxysm and has been passed through 8 rats and one mouse The chief differences between the strains consist in the fact that B was more recently obtained from its human host and that it has had a shorter residence in animals Clinically the patients supplying these two strains had the isthmian type of fever Morphologically there are no differences between the two strains of spirochetes Parallel inoculations of strains A and B into animals immunized to A have been made, with the result that animals which had recovered from an infection by A could be infected by B, yet would be immune to A The period of incubation was sometimes prolonged and the number of spirochetes few, yet, on the other hand, the infection by B in two animals immunized to A was prompt and severe, and in one—Rat 67—the infection by A in an animal immunized to B was also prompt and severe

In this experiment a rat infected by and presumably immune to strain B was promptly infected by strain A nine days after the disappearance of strain B This proves that the difference in the activity of the strains is not one of relative virulence, but is due to there being specific strains with specific immunizing powers This is the most important fact developed in the course of the investigation and is of the greatest value in connection with any attempts to derive a curative or preventive serum, it is suggestive in explanation of the fact mentioned by Vandyke Carter and others that one attack of relapsing fever does not confer a high degree of immunity for an individual becoming infected by one strain in a given locality might well be non-immune with regard to other strains in that locality

TABLE 5 —IMMUNITY AND INFECTION IN MICE 17 AND 13

Mouse 17, inoculated Nov 23, '07 from Mouse 13, when No 13 had 1 spirochete to 10 fields   Immediately after the inoculation 5 c c blood was drawn from Rats 1 and 7, which had an infection, and injected subcutaneously into Mouse 17 (Passive Immunity Experiment)

Mouse 13, inoculated Nov 12 from Mouse No 12 when No 12 had fewer spirochetes than 1 to 500 fields

11/24—No spirochetes in 300 fields	11/13—No spirochetes in 300 fields
11/25—No spirochetes in 300 fields	11/14—No spirochetes in 300 fields
11/26—No spirochetes in 300 fields	11/15—No spirochetes in 300 fields
11/27— 1 spirochete in 5 fields	11/16—No spirochetes in 300 fields
11/28— 1 spirochete in 1 field	11/17— 1 spirochete in 14 fields
11/29—No spirochetes in 300 fields	11/18— 1 spirochete in 75 fields
11/30—No spirochetes in 300 fields	11/19—No spirochetes in 300 fields
12/ 1—No spirochetes in 300 fields	11/20—No spirochetes in 300 fields
12/ 2—No spirochetes in 300 fields	11/21—Not examined
12/ 3—No spirochetes in 300 fields	11/22—No spirochetes in 300 fields
12/ 4— 1 spirochete in 100 fields	11/23— 1 spirochete in 10 fields
12/ 5— 1 spirochete in 300 fields	11/24—No spirochetes in 300 fields
12/ 6— 1 spirochete in 100 fields	11/25—No spirochetes in 300 fields
12/ 7—No spirochetes in 300 fields	11/26—No spirochetes in 300 fields
12/ 8—No spirochetes in 300 fields	11/27—No spirochetes in 300 fields
12/ 9—No spirochetes in 300 fields	11/28—No spirochetes in 300 fields
12/10—No spirochetes in 300 fields	11/29—No spirochetes in 300 fields
12/11— 1 spirochete in 69 fields	11/30— 1 spirochete in 300 fields
12/12— 1 spirochete in 20 fields	12/ 1—No spirochetes in 300 fields
12/13— 8 spirochetes in 100 fields	12/ 2—No spirochetes in 300 fields
12/14—No spirochetes in 300 fields	12/ 3—No spirochetes in 300 fields
12/15—No spirochetes in 300 fields	12/ 4—No spirochetes in 300 fields
12/16—No spirochetes in 300 fields	12/ 5—No spirochetes in 300 fields
12/17—No spirochetes in 300 fields	
12/18—No spirochetes in 300 fields	
12/19—No spirochetes in 300 fields	
12/20—No spirochetes in 300 fields	
12/21—No spirochetes in 300 fields	

TABLE 6 —INFECTION AND IMMUNITY IN MICE B 8 (17) AND 61 (13)

January 28, Mouse 17 (which became Mouse B-8) inoculated from B 5 when B 5 had 14 spirochetes to 100 fields using citrated heart's blood intraperitoneally

January 28, Mouse 13 (which became Mouse 61) inoculated with citrated blood from the heart of No 59 when 59 had 18 spirochetes to 10 fields

1/29—No spirochetes in 300 fields	1/29—No spirochetes in 200 fields
1/30—No spirochetes in 300 fields	1/30—No spirochetes in 200 fields
1/31—No spirochetes in 300 fields	1/31—No spirochetes in 200 fields
2/ 1— 4 spirochetes in 100 fields	2/ 1—No spirochetes in 200 fields
2/ 2— 7 spirochetes in 100 fields	2/ 2—No spirochetes in 400 fields
2/ 3— 2 spirochetes in 100 fields	2/ 3—No spirochetes in 200 fields
2/ 4—No spirochetes in 300 fields	2/ 4—No spirochetes in 200 fields
2/ 5—No spirochetes in 300 fields	2/ 5—Not examined
2/ 6—No spirochetes in 300 fields	2/ 6—No spirochetes in 200 fields
2/ 7— 1 spirochete in 200 fields	
Sacrificed	

In this experiment the mouse, while having an actively acquired immunity to Strain A, was infected by Strain B   Controlled by Mouse 61 (13)

In this experiment the mouse having an actively acquired immunity to Strain A was still immune after 59 days to Strain A   Control to Mouse B 8 (17)

Rats 36 and 37, immunized to strain A, having had spirochetes in their blood on December 21 for the last time, were inoculated on January 24 by strain B The animals inoculated by strain B showed a prompt and severe infection

TABLE 7 —COURSE OF INFECTION IN RATS 36 AND 37

Rat 36, inoculated December 18, p m from Rat 30 when No 30 had 148 spirochetes to 100 fields, using citrated heart's blood intraperitoneally

Rat 37, inoculated December 18 p m from Rat 30 when No 30 had 148 spirochetes to 100 fields, using citrated heart's blood intraperitoneally

12/19— 13 spirochetes to 100 fields	12/19— 8 spirochetes to 100 fields
12/20—220 spirochetes to 100 fields	12/20—140 spirochetes to 100 fields
12/21—360 spirochetes to 100 fields	12/21—120 spirochetes to 100 fields
12/22—No spirochetes to 300 fields	12/22—No spirochetes in 300 fields
12/23—No spirochetes to 300 fields	12/23—No spirochetes in 300 fields
12/24—No spirochetes to 300 fields	12/24—1 atypical spirochete in 300 fields
12/25—No spirochetes to 300 fields	12/25—No spirochetes in 300 fields
12/26—No spirochetes to 300 fields	12/26—No spirochetes in 300 fields
12/27—No spirochetes to 300 fields	12/27—No spirochetes in 300 fields

TABLE 8 —COURSE OF INFECTION IN RATS B 3 (36) AND B 4 (37)

January 24, Rat 36 (which became Rat B 3), inoculated with Strain B from Rat B-1 when B-1 had 8 spirochetes to 1 field, using citrated heart's blood intraperitoneally

1/25—18 spirochetes to 10 fields

January 24, Rat 37 (which became Rat B 4) inoculated from Rat B 1 when B 1 had 8 spirochetes to 1 field, using citrated heart's blood intraperitoneally

1/25—43 spirochetes to 10 fields
1/26—10 spirochetes to 1 field
1/27—No spirochetes to 300 fields
1/28—No spirochetes to 300 fields, died

Furthermore a rat (B 2) immunized to strain B was inoculated eight days after the disappearance of spirochetes from his peripheral blood, with spirochetes from Rat 53, strain A The rat became infected within twenty four hours and experienced a moderately severe infection

TABLE 9 —COURSE OF INFECTION IN RAT B 2

Rat B 2, inoculated Jan 24 from No B-1 when the latter had 8 spirochetes to 1 field, using citrated saline heart's blood intraperitoneally

1/25— 2 spirochetes to 1 field
1/26— 20 spirochetes to 1 field
1/27—No spirochetes to 300 fields
1/28—No spirochetes to 300 fields
1/29—No spirochetes to 300 fields
1/30—No spirochetes to 300 fields

1/31—No spirochetes to 300 fields
2/ 1—No spirochetes to 300 fields
2/ 2—No spirochetes to 300 fields
2/ 3—No spirochetes to 300 fields
2/ 4—No spirochetes to 300 fields

TABLE 10 —COURSE OF INFECTION IN RAT 67 (B 2)

2/4—Inoculated Rat B 2 (which became Rat 67) from Rat 63, Strain A, when the latter had 210 spirochetes per 100 fields using citrated neck blood intraperitoneally

2/5— 25 spirochetes to 100 fields
2/6—340 spirochetes to 100 fields
2/7— 32 spirochetes to 100 fields

PASSIVE IMMUNITY

Two attempts have been made to produce passive immunity by the subcutaneous injection of blood from a convalescent animal a moment after infected blood had been injected intraperitoneally

Mouse 17, inoculated December 23 from Mouse 13, when the latter had one spirochete in 10 fields Immediately afterward blood was drawn from the tail of Rat 7, formerly No 1, 0 5 c c of blood being used and injected subcutaneously Rat 7, formerly No 1, had been infected with human blood strain A October 11, and was subsequently inoculated with blood from infected Mouse 2 This quantity of blood from an animal which had recovered was not sufficient to prevent a severe infection in Mouse 17 with three paroxysms after an incubation period of four days

Rat 45, inoculated December 27, from Rat 41, when the latter had 450 spirochetes to 100 fields inoculation intraperitoneal followed by a subcutaneous injection of 5 drops of heart's blood from Rat 31, whose blood had been free from spirochetes for nine days This quantity of blood from a convalescent was not sufficient to prevent Rat 45 becoming infected after a period of forty eight hours

Blood from convalescents, therefore, in the quantities used is of no value in preventing an infection The period of incubation however, as in Rat 45 and Mouse 17, may be prolonged

In these experiments very large amounts of infected blood were not used in the attempts to infect or reinfect animals Only that quantity was used which was amply sufficient to cause the disease in a susceptible

non-immune animal   When very large quantities of blood are used the contained spirochetes become disseminated through the blood stream of the inoculated animal, they are merely diluted and their presence does not positively mean that they have multiplied within the blood stream

HYPERIMMUNITY PREVENTION

A goat has been gradually hyperimmunized, in addition to its natural immunity, by successive injections of infected white rat's blood, containing strains A and B, and one injection of blood from human source (Case 1)   In all, 11 subcutaneous injections of infected blood have been given from three human sources

TABLE 11 —INOCULATIONS RECEIVED BY GOAT

Inoculation Blood From—	Inoculation Blood From—
7/31, 1907—Lindoff, Case 1	1/ 2, 1908—Rat 46, Strain A
12/ 6, 1907—Rat 21, Strain A	1/11, 1908—Rat 49, Strain A
12/12, 1907—Rat 24, Strain A	1/16, 1908—Rat 51, Strain A
12/15, 1907—Rat 26, Strain A	1/24, 1908—Rat B-1, Strain B
12/24, 1907—Rat 38, Strain A	1/28, 1908—Rat 59, Strain A
12/27, 1907—Rat 41, Strain A	

Serum was collected from this goat February 6, 5 p m , placed in a refrigerator at 51 degrees F until the following afternoon, when it was used in the two following experiments

Mouse 68, inoculated February 7, 3 p m , from Rat 66, which had 90 spiro chetes to 100 fields, using citrated peripheral tail-blood, 2 drops intraperitoneally, followed immediately by an intraperitoneal injection of 5 c c of hyperimmune goat serum   Spirochetes appeared in Mouse 68 on February 13, 2 spirochetes to 100 fields, or after the prolonged incubation period of six days   Most of the mouse s red blood corpuscles were diminished in size, strongly resembling goat s red blood corpuscles, the larger red blood corpuscles showed considerable poly chromatophilia and fine granulations, but no basophilic granulation was noticed

TABLE 12 —COURSE OF INFECTION IN MOUSE No 68

Date of Inoculation 1908	Notes
February 7, 3 p m	
February 8	
February 9	
February 10—No spirochetes in 400 fields	most of the red blood corpuscles are small—goat size and the larger ones show polychromatophilia and granular degeneration—no basophilia
February 11—No spirochetes in 300 fields	Red blood corpuscles same as on the 10th
February 12—No spirochetes in 300 fields	Polychromatophilia increased , 60 per cent of the r b c are polychromatophilic R b c increasing in size
February 13— 2 spirochetes to 100 fields	
February 14—24 spirochetes to 100 fields	
February 15—No spirochetes to 300 fields	
February 16—No spirochetes to 300 fields	Polychromatophilia still marked R b c normal size
February 17— 2 spirochetes to 100 fields	
February 18—16 spirochetes to 100 fields	
February 19—12 spirochetes to 100 fields	Polychromatophilia diminishing R b c normal size Died Spleen enlarged Autopsy otherwise negative

TABLE 13 —COURSE OF INFECTION IN MOUSE 69

Date of Inoculation 1908	Notes
February 7	(3 p m)—From Rat No 66, when the latter had 90 spirochetes to 100 fields, using 2 drops of citrated tail blood, followed by a subcutaneous injection 0 7 c c hyperimmune goat serum
February 8	
February 9—No spirochetes in 300 fields	
February 10—No spirochetes in 300 fields	Blood shows many small goat size r b c The larger normal size corpuscles are polychromatophilic and finely granular
February 11—No spirochetes in 300 fields	
February 12—No spirochetes in 300 fields	
February 13—20 spirochetes in 100 fields	
February 14—No spirochetes in 400 fields	
February 15—No spirochetes in 300 fields	
February 16—No spirochetes in 300 fields normal size	Polychromatophilia still marked R b c
February 17— 3 spirochetes to 100 fields	
February 18—12 spirochetes to 100 fields	
February 19— 1 spirochete to 300 fields	
February 20—No spirochetes to 300 fields normal size	Polychromatophilia much diminished R b c
February 21— 1 spirochete to 300 fields	
February 22—No spirochetes to 300 fields—and none in 5 successive daily examinations	

In this experiment the period of incubation was greatly and equally prolonged in both mice, although Mouse 68 received about seven times as much serum as Mouse 69, and this intraperitoneally Mouse 68 died during the second paroxysm, while Mouse 69 had a light primary paroxysm and a very mild secondary paroxysm There was considerable blood destruction in each mouse The supply of rats became exhausted at this time, so that it was not possible to increase the immunizing substances in the goat serum A serum of this strength and character, in the quantity used, apparently merely prolongs the period of incubation, for, after the injection of the hyperimmune serum, the immunizing substances are very possibly slowly eliminated or rendered inert, the spirochetes then multiply as in an animal receiving a minimum amount of infected blood without the addition of immune serum

It was necessary to use white mice in this experiment so as to avoid excessive hemolysis, the goat having been immunized with infected white rat's blood, which had rendered the goat serum hemolytic for the red blood corpuscles of the white rat

HEREDITARY IMMUNITY

No opportunity arose for making observations on the immunity resulting from infection through the placenta

PREVENTION BY VACCINATION

The results of experiments on the immunization of rats and mice with strains A and B show conclusively that curative or preventive serums, if derived at all. must be obtained by the inoculation of several strains Polyvalent serums must be used and the question arises as to

whethei it will be necessaiy to hypeiimmunize an animal to each of the stiains or whether, peihaps, single inoculations of a laige numbei ot stiains may be sufficient to hypeiimmunize

A method of treatment not yet investigated is that of vaccination This is suggested on account of the fact that phagocytosis plaɟs an important pait in the piotective mechanism against the infection In the investigation of this question it will be necessaiy to devise a piacticable method for the cultivation of the spiiochetes

INFLUENCE ON THE INFECTION OF DRUGS ADMINISTERED HYPODER-
MICALLY

A few experiments were cariied out to determine the influence, if any, of certain aniline dyes and other substances on the course of the disease in iats The following substances weie used

        Neutral red
        Congo red
        Orcein
        Saffranin
        Bordeaux red
        Sulphanilic acid
        Quinin and urea hydiochloiate
        Methylene blue

Satuiated solutions of these substances in noimal saline solution weie injected subcutaneously immediately after a peiitoneal injection of infected blood had been given A control rat was always inoculated at the same time The result of such injection in almost every instance was an earlier and moie seveie infection than in the contiol rat which had not been tieated with the dyes

Methylene blue, when given in veiy large doses, prevented an infection, but the animals were piofoundly poisoned bɟ the diug and died on the second and thiid day Dilute solutions of methylene blue weie of no value in pieventing an infection The minimal piotective dose of methylene blue could not be woiked out at this time, but the use of methylene blue and allied substances seems to affoid a faʌoiable line foi investigation

In two experiments with orcein such heavy infections followed that it was thought that orcein might bieak down an activelɟ acquired immunitɟ, accordingly Rat 27, having passed thiough an infection between Decembei 13 and 15, was inoculated from infected Rat 38 and tieated hypodermicallɟ with 10 diops of saturated solution of orcein in noimal saline solution, the animal failed to become infected Orcein,

therefore, in the quantity used can not destroy an actively acquired immunity

PARALLEL INFECTION WITH SPIROCHETES AND TRYPANOSOMA LEWISI, IN MUS RATTUS

There is no striking modification of a trypanosomal infection in rats by the parallel infection with spirochetes, nor, on the other hand, are the spirochetes affected by the presence of trypanosomes In one instance (Rat 56) the trypanosomes increased at equal pace with the spirochetes, but the trypanosomes remained in the blood continuously for weeks after the spirochetes had disappeared   (See Fig 9, chart of parallel infection of trypanosomes and spirochetes)

TRANSMISSION OF RELAPSING FEVER

The transmission of African relapsing fever by means of infected ticks, *Ornithodoros moubata,* from monkey to monkey was accomplished by the late T Everett Dutton and John S Todd of the Liverpool School of Tropical Medicine in 1904   During the next year infected ticks were sent to Liverpool, and from these ticks monkeys were infected   Dutton and Todd were also successful in transmitting the spirochetes by the bites of young ticks newly hatched in the laboratory from eggs laid by infected parents

Breinl, Kinghorn and Todd were unsuccessful in their attempts to transmit *Sp duttoni* or *Sp obermeieri* from monkey to monkey by means of bedbugs   The analogous disease in fowls, as determined by Marchoux and Salimbeni,[24] is transmitted by a tick, *Argus miniatus*

In an interesting note concerning the earliest mentioned epidemics in Great Britain Begbie quotes Welsh, who wrote from Edinburgh in 1819, as follows

When acting as a clerk in the Royal Infirmary, in the course of four months my three colleagues, two of the young men in the apothecary shop, two housemaids and thirteen or fourteen nurses caught the disease and the matron and one of the dressers died of it   Since I left the Infirmary three more of the gentlemen acting as clerks, one of the young men in the shop and many more of the nurses have caught the infection   When it begins in a family we always expect more than one of them to be affected   I could mention instances of 4, 5, 6 and 7 being sent to the hospital out of one family, 8, 9 and 10 out of one room, 20 and 30 out of one stair and 30 and 40 out of one close, and this all in the course of a few months   Hardly any of the nurses, laundry women or others coming in contact, either with the patients or their clothes, have escaped   At one time there were 18 nurses off duty from the fever   It appears sufficiently remarkable that, as specially noted by Dr Connant in 1843 and 1844, laundry women engaged in washing the clothes of the sick, though never brought into direct communication with the patients themselves, suffered frequently from the disease

24 Marchoux E, and Salimbeni A   Ann de l'Inst Pasteur 1903 XVII, 569

After reading the accounts of epidemics of relapsing fever, together with our knowledge of the mode of transmission of tick fever and spirillosis in fowl and Mackie's observations in India, one can hardly escape the belief that the spirochetes of our local relapsing fever are conveyed mechanically or by an intermediary host in the person of some suctorial insect or acarid—fleas, bedbugs, ticks, lice or mosquitoes   The disappearance of relapsing fever for long periods after extensive epidemics from some localities, such as Scotland and Ireland, the failure of the disease to assume any extensive character in the United States and certain other places after introduction, and the limitation of the disease frequently to recently arrived immigrants or sailors and to seaport or neighboring towns, point strongly to a suctorial insect as the agent of transmission, and render it highly probable that the conditions for the existence of this host are not favorable in the United States and certain other places, either due to the fact that the suctorial host does not survive, or that it does not possess a suitable alternate host to subsist on when man is not available

There is no evidence to prove the necessity of contact as in syphilis or in dourine or *mal de coit,* the trypanosomal disease of horses transmitted during copulation   Inoculation is accomplished with ease, for in two laboratories where animal inoculations have been made with *Sp duttoni* and *Sp obermeieri* two investigators and three assistants have been infected through an abraded skin during an autopsy on a severely infected monkey and by the bites of infected monkeys   Recently Mackie, of Bombay, has made an important contribution to our knowledge of the transmission of *Sp carteri* by *Pediculus corporis*   Mackie studied an outbreak of Bombay relapsing fever at the Nasik Mission Settlement   He found that 14 per cent of lice taken from the heavily infected boys' ward, 2 per cent taken from the scantily infected girls' ward and 13 per cent of artificially fed lice showed multiplication of spirilla in internal organs

Attempts have been made at the laboratory here to infect animals by means of ticks, but all efforts have been unsuccessful   At the suggestion of Mr C L Marlatt, of the Department of Agriculture several specimens of *Amblyomma*[25] were tied with rats   These ticks, *Amblyomma dissimile,* taken from iguanas, and *Amblyomma cajennense,* taken from dogs, have long biting parts and are dislodged from their cus-

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25 During excursions out into the bush and jungle, I find that specimens of *Amblyomma* (species undetermined) larval and adults, readily attach themselves and feed voraciously

tomary host with difficulty, but they are probably too large to be used in the transmission experiments with rats

The ecto-parasites of rats are generally quite small, fleas, mites and small ticks The common dog tick of Panama, *Rhipicephalus texanus,* has shorter biting parts and is more easily dislodged This tick will attach itself to rats, but unless the rat is immobilized the ticks are rapidly killed and eaten

CONCLUSIONS

The relapsing fever of Panama is distinct from the analogous fever of Africa, Europe and Asia, although belonging to the same general class

The micro-organism causing the local relapsing fever belongs to the group containing *Sp obermeieri, Sp duttoni* and *Sp carteri*

This spirochete causes a recurring infection in man, monkeys (genus *Macacus*) and white mice, and single paroxysms in white and wild rats

The animal reactions are similar to those obtained by Norris, Pappenheimer, Fleurnoy, Novy and Knapp, with the organism erroneously identified by the latter two as *Spirillum obermeieri*

The blood of animals very recently recovered from an infection and that between paroxysms, where spirochetes are apparently absent from the peripheral blood, is infectious, and by analogy this affords a valuable means of diagnosis of the fever in man during the afebrile period by the inoculation of susceptible animals, mice and rats with patient's blood

There is considerable variation in the morphology of the spirochete in the same strain and sometimes in the same smear

Identification of spirochetes can not be made with certainty on morphologic grounds

The mechanism of defense is largely that of phagocytosis by hepatic endothelium

Infected animals sacrificed at different stages of the infection show, as the disease advances, an increasing number of fragmented spirochetes, engulfed by endothelial cells of the liver

In animals which had recently recovered from an infection a liver emulsion is more infectious than heart's blood This suggests the probable vitality and unity of fragments

Infection by one strain of spirochetes is followed by a considerable degree of active immunity for that strain, but such immunity is not potent against another strain from a different source, although of the same species and from the same locality but from a different human host

For the production of preventive and curative serums polyvalent sera derived from all the strains will probably be necessary

The blood, in moderate amounts, of subjects which have recovered, is of no value in preventing infections in white mice and white rats

Relapses may be explained by the multiplication of spirochetes in out-of-the-way places where they do not enter the portal circulation and can not be engulfed by liver endothelium

Agglutination of spirochetes occurs at least twenty-four hours before the crisis in rats *in vitro* and *in vivo*

This spirochete is probably a spiral ribbon and not a spiral cylinder

The group of spiral-shaped micro-organisms needs reclassification on a basis of morphology, pathogenity and habitat

This spirochete is more closely related to bacteria than to protozoa

The rôle of the spleen is similar to that observed in anemia

With suitable emulsions of liver substance and immune serums it should be possible to demonstrate specific opsonins

The natural mode of infection is probably by means of an intermediary host—some suctorial insect or acarid, either directly or by means of an alternate host, such as a wild rat or other susceptible animal

REPORT OF A CASE OF STOKES-ADAMS' DISEASE

THEODORE B BARRINGER, JR, M D
NEW YORK

This case presents several interesting features, similar instance which have not as yet been reported

Patient —A blacksmith was admitted to the wards of the fourth me division of Bellevue Hospital, suffering from acute gout, involving the and large toe joints He had had several previous attacks of gout and tw years earlier a chancre with well-marked secondary symptoms He had alcohol to excess for years He also complained of attacks of vertigo syncope

Physical Examination —An obese man, five feet seven inches tall, some dyspneic The apex beat is in the fifth left interspace, four and one half in from the median line, and distinctly heaving The outlines of the heart difficult to determine on account of the thick chest wall The heart retio slow and regular, 44 to the minute, and the sounds are normal except for accentuated aortic second At the aortic area a systolic murmur is heard tr mitted upward There are no sounds heard during the diastolic pause radial pulse is 44 to the minute and of increased tension (the systolic pres varied between 160 and 170) The radials and brachials are sclerosed edge of the right lobe of the liver is felt three inches below the ribs in mammary line

The tracings shown in Figures 1 and 2 were taken from the apex beat, 1 and radial artery It will be seen that the auricular rhythm bears no cons relation to the ventricular rhythm, that is, the patient is suffering from c plete auriculoventricular dissociation At the time these particular rec were taken, the auricular rate was 69 and the ventricular rate 39 per min

The marked auricular liver pulse is unusual in cases of heart block an probably a coincidence, having nothing to do with the essential heart les Its significance is doubtful Mackenzie believes it to be due, in a majority cases, to tricuspid stenosis

The patient remained under treatment for several months During time he had three attacks of vertigo and two syncopal attacks, once falling cutting his forehead Unfortunately, he was not seen until some minutes a each of these attacks, so I could not tell if they were preceded by a slow of the ventricles

The condition of complete dissociation continued for a week after adi sion and then gradually disappeared, the pulse increasing through several d until it reached 68 to 80 per minute After a few days of normal rate the bl again returned gradually and persisted a few days His longest period of ble ing was ten days, and his longest period of normal rate was three weeks several occasions, as was to be expected, the tracings showed a partial bl with two to one rhythm During his normal period the auriculoventricu interval was not lengthened, and the auricular liver pulse persisted

Atropin has been used by a number of observers in cases of heart-block to test the degree of dissociation Its usually observed mode of action is as follows In complete block the auricular rate is markedly increased, while the ventricular rate is practically uninfluenced In partial block, where some of the auricular impulses pass over to the ventricle, atropin increases the auricular rate, and therefore the number of transmitted auricular stimuli, and so the ventricular rate The usual explanation of this action of atropin is that it paralyzes the terminal cardiac filaments of the vagus nerve, which presumably exist only in the auricles So atropin, or any measure acting on the vagus nerve, can in-
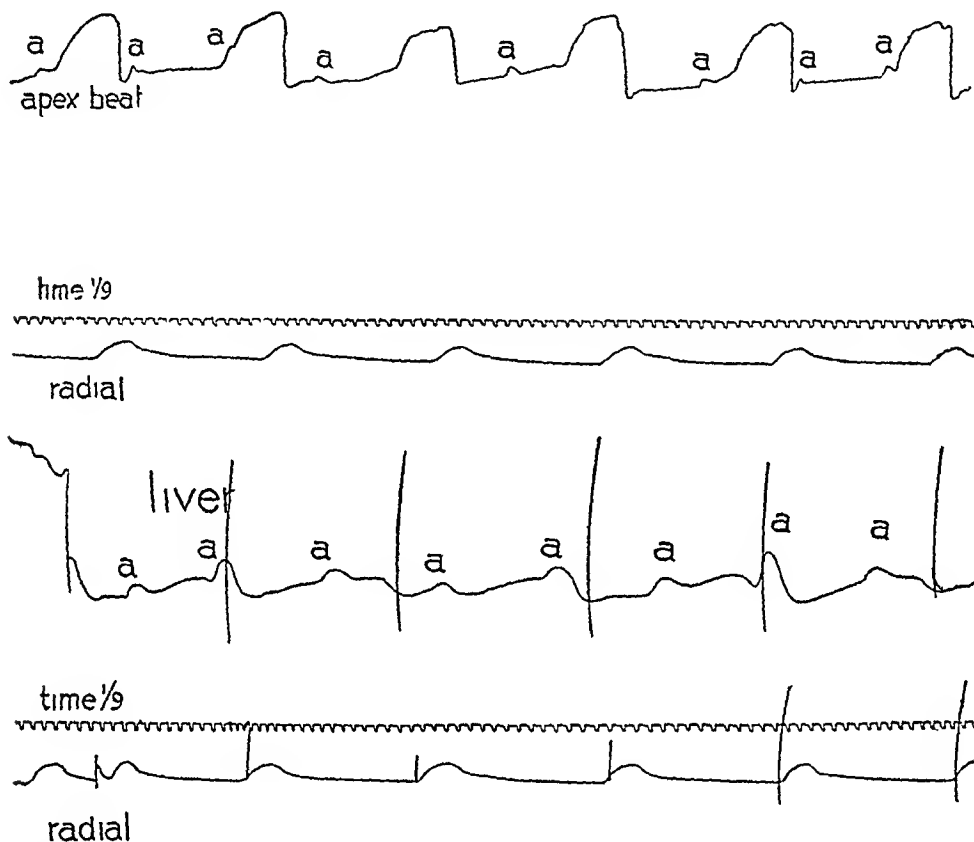

Figs 1 and 2 —Tracings from apex beat, liver and artery The letter *a* represents waves due to the contraction of the left auricle in the apex tracing, and the right auricle in the liver tracing

fluence the ventricle only indirectly, provided, of course, that the auriculoventricular bundle is capable of transmitting the impulse

Tabora[1] has shown, however, in the course of some experiments with the action of digitalis on dogs, that the vagus nerve has a markedly elective influence on the conductivity of the auriculoventricular bundle If this view is correct, a case such as ours with an auriculoventricular

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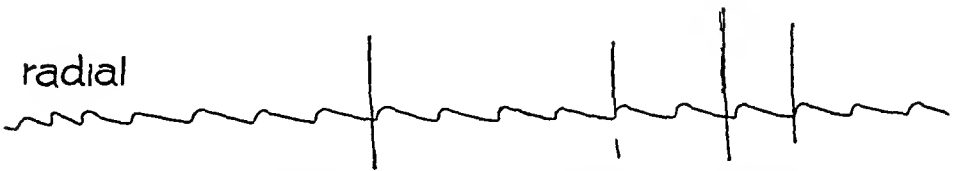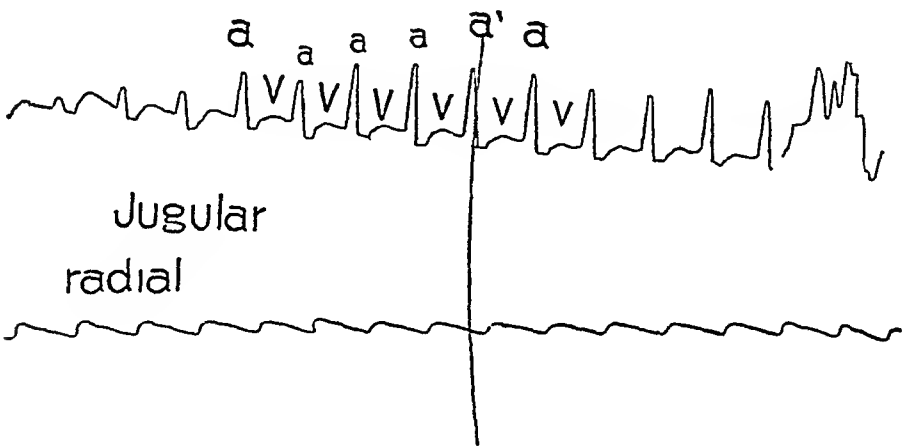1 Tabora Ztschr f exper Path u Therap , 1906 iii, 549
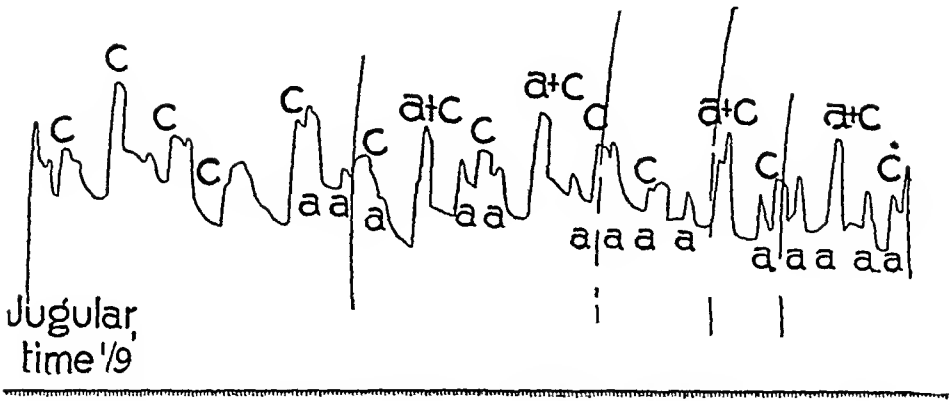
Fig 3 —Tracing showing auriculoventricular dissociation

Fig 4 —Diagram from Figure 3, upper lines, reconstructed c waves, lower lines, reconstructed a waves

Fig 5 —Tracing taken after administration of atropin

bundle showing marked variations in its conductivity, ought to be very favorably influenced by atropin, which would remove this inhibitory vagus effect This experiment was accordingly carried out

The tracing shown in Figure 3 was taken at 2 10 p m For five days previous, a condition of partial or complete block had existed, the pulse varying between 40 and 50 per minute This shows a complete dissociation, with a ventricular rate of 39 and an auricular rate of 59 per minute The absence of relation between auricular and ventricular systoles is recognized more easily in the diagram (Figure 4) constructed from the tracing

At 2 12, 1/50 gram of atropin was given by hypodermic injection At 2 27 the pulse rate had increased to 61, and at 2 47 the tracing shown in Figure 5 was taken

This shows an absence of block with auricular and ventricular rate of 74 to the minute That evening the radial pulse was 44 per minute, and for the next thirty-six hours from 44 to 48 per minute

This experiment supports the view that the vagus nerve influences the conductivity of the auriculoventricular bundle It shows, moreover, that atropin can not always be depended on to determine whether a block is complete or not Tabora[1] also demonstrated in his experimental work that vagus action alone can not produce dissociation an additional factor is necessary, either anatomical change in the auriculoventricular bundle or a damaging of its conductivity

Consideration of this experimental work, together with the age of our patient, his arteriosclerosis, and the history of syphilis, make it probable that there was some morphological change in the auriculoventricular bundle The inhibitory action of the vagus on the damaged bundle decreased its conductivity so much further that the varying degrees of dissociation were produced

I am indebted to Dr Alexander Lambert for the privilege of reporting this case

34 West Eighty-fourth Street

BOOK REVIEW

The early appearance of a second American edition of Sahli's Diag-
nostic Methods is evidence of the usefulness and popularity of this excel-
lent work, the special strength of which lies probably in the fact that,
as pointed out by the author in the preface, it is not a mere compilation
One may indeed turn to most of the sections and find a good discussion
of diagnostic methods by a wise and experienced observer   It is a well-
rounded work in which the personal experience of the author is evident
at many points

Nothing could be sounder than the remarks on percussion (page 154)
and the statement that "   the percussion note which is loud
enough to be heard at considerable distance is generally faulty"   The
observation on page 265 apropos of auscultation of the heart that "we
should always auscultate the patient in different positions, particularly
standing and lying down," is too often forgotten

A large section (pp 397 *et seq*) is devoted to a detailed description
of the Sahli-Seiler butyrometric method of examination of the gastric
functions   The terminal section on diseases of the nervous system is
extensive and useful

The book is so well known that an extended review is not necessary

Professor Sahli has been happy in the editors of the American edi-
tion   The translation is good, the remarks which have been added by the
American editors are often helpful and many of the new illustrations
are excellent and real additions to the work

A few minor notes of suggestion or criticism may not, however, be
out of place

It is a pity that a more thorough description of the venous pulse
should not have been included in the section on examination of the heart
and vessels, and again, although in the supplement some of Wenckebach's
work has been reviewed, one misses the judicious summary of modern
researches so valuable in other parts of the work

The description of the cardiogram (p 298) is not what might be desired It is also rather surprising (pp 177-8) that so good an observer as the author should fail to recognize the ease with which the right heart may be outlined by careful percussion in most cases Indeed, the diagrams on these two pages are not wholly in conformity one with another

The illustration introduced by the American editors on page 181 is hardly happy In the experience of the reviewer percussion has never given so obtuse a cardio-hepatic angle excepting in pericardial effusions

M Huchard would probably be somewhat surprised to find himself referred to on p 260 as "von Huchard"

It would be well if the terminology of animal parasites should be brought into concordance with the now recognized rules of zoological nomenclature There would seem to be small reason to-day for the doubt expressed on p 435 as to the pathological significance of *Strongyloides stercoralis,* which is here called incorrectly *Anguillula intestinalis* and *stercoralis* Again, it would have been well for the American editors to point out the rarity of *Tænia solium* in the United States

In the section on examination of the blood no mention is made of the very valuable modifications of Romanovsky's stain, such as Leishman's, Wright's and Hastings'

The reviewer can not agree with the author in his advice that the term "Hodgkin's disease" be dropped The observations of Dorothy Reed would seem to justify the classification of this variety of disease of the lymphatic apparatus as an entity either as Hodgkin's disease or lymphadenoma

It would have been wise to omit all reference to exploratory puncture in appendicitis (p 725) or to condemn it unreservedly

There are many, assuredly and among these is the reviewer, who will regret that in this otherwise excellent translation a somewhat prevalent but most unlovely fashion has been followed of omitting the terminal "al" from certain adjectives Such adjectives as "cylindric," "anatomic," "tropic," "symmetric,' "hysteric' and the like do not beautify or simplify the English language But these are small criticisms of an excellent work—one of the best existing manuals of diagnosis

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THE EFFECTS OF CUTTING THE BRANCH OF THE HIS BUNDLE GOING TO THE LEFT VENTRICLE [*]

LEWELLYS F BARKER, M D , AND A D HIRSCHFELDER, M D

BALTIMORE

The idea that under certain conditions the two ventricles do not beat absolutely synchronously is an old one, and was used by C J B Williams and by Skoda[1] to explain the production of split heart sounds Experimental evidence of this asynchronism was given in 1890 by Philipp Knoll,[2] who showed that the right ventricle contracted before the left during vagus stimulation Knoll's experiments were confirmed by Léon Fredericq[3] (1906) and his pupil Stassen[4] (1907) The latter showed that if ventricular extrasystoles were produced while the vagi were being stimulated, the ventricle in which the extrasystole was produced contracted 0 02 to 0 03 second before the other ventricle

The idea that under certain conditions the action of the two ventricles might be so completely dissociated that a contraction of the one might be said to occur without the contraction of the other, was proposed by von Leyden[5] in 1868 to explain a case of arrhythmia. in which one small beat followed a few tenths of a second after the regular beats

Von Leyden believed that the large beat corresponded to systole of one ventricle, the small beat to systole of the other Indeed, his curves showed that, though the first of the two beats gave a larger impulse over the apex, the second of the two gave a larger impulse over the right ventricle Von Leyden's explanation has been questioned by Riegel,[6]

[*] From the Medical Clinic of the Johns Hopkins Hospital and University

1 Williams and Skoda, quoted from von Leyden

2 Knoll, Philip Ueber Incongruenz in der Thätigkeit der beiden Herzhälften Sitzungsb d k Akad d Wissensch Math-natuw Cl, Vienna 1890 xciv 31 53, 6

3 Fredericq, Leon La pulsation du cœur du chien est une onde de contraction, etc Arch internat de physiol 1906 iv, 60

4 Stassen M De l ordre de succession des différentes phases de la pulsation cardiaque chez le chien Arch internat de physiol 1907 v 600

5 von Leyden E Ueber ungleichzeitige Kontraction beider Ventrikel Arch f path Anat 1868 xliv 365

6 Riegel F Zur Lehre von der Herzirregularität und Inkongruenz in der Thätigkeit der beiden Herzhälften Wiesbaden 1891

Hering,[7] Helsingius,[8] and a host of others who claim that the condition present was simply a pulsus bigeminus of extrasystolic origin   If this explanation is true, it would follow that over certain parts of the heart especially over the right ventricle, the movement due to the extrasystoles was more marked than that due to the strong regular beat   This paradoxical effect might be due to the relation of the heart to the ventricle in the particular intercostal space during the extrasystole
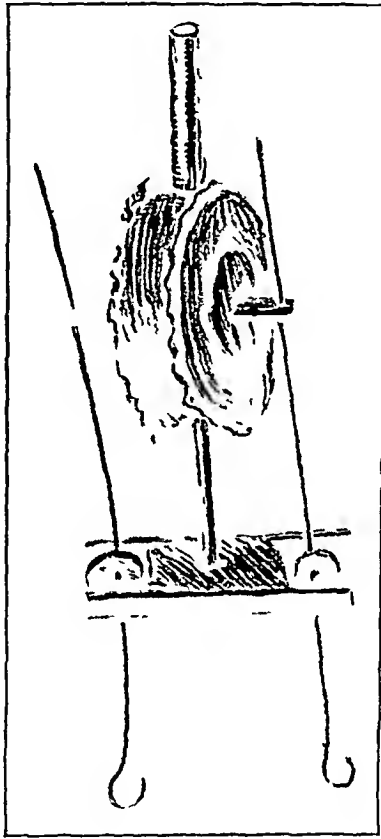
Fig 1 —An transmission myocardiograph

In 1907 Kraus and Nicolai[9] reported a case in which they believed that complete dissociation of the ventricles was present   and claim to

7 Hering H E   Pseudo Hemisystole und postmortale Hemisystole Deutsch med Wchnschr   1903 xxix 381

8 Helsingius O F   Zur Frage der Leidenschen Hemisystolie   Deutsch med Wchnschr   1906 xxxii 1406

9 Kraus F   und Nicolai G F   Ueber das Elektrocardiogramm unter normalen und pathologischen Verhaltnissen   Berl Klin Wchnschr   1907 xliv, 765

Ueber die funktionelle Solidaritat der beiden Herzhalften   Deutsch med Wchnschr   1908 xxxiv 1

have shown it by electrocardiograms, though, as far as we know, they
have not published the curves taken   In 1908 Hewlett[10] reported a case
in which beats appeared on the jugular pulse which could not be seen on
either the apex or the radial tracing   He believed that these curves
on the jugular tracing represented systoles of the right ventricles unac-
companied by systoles of the left, and, moreover, notes that in many
cases the interval between the cardiogram and jugular wave is subject to
considerable variations
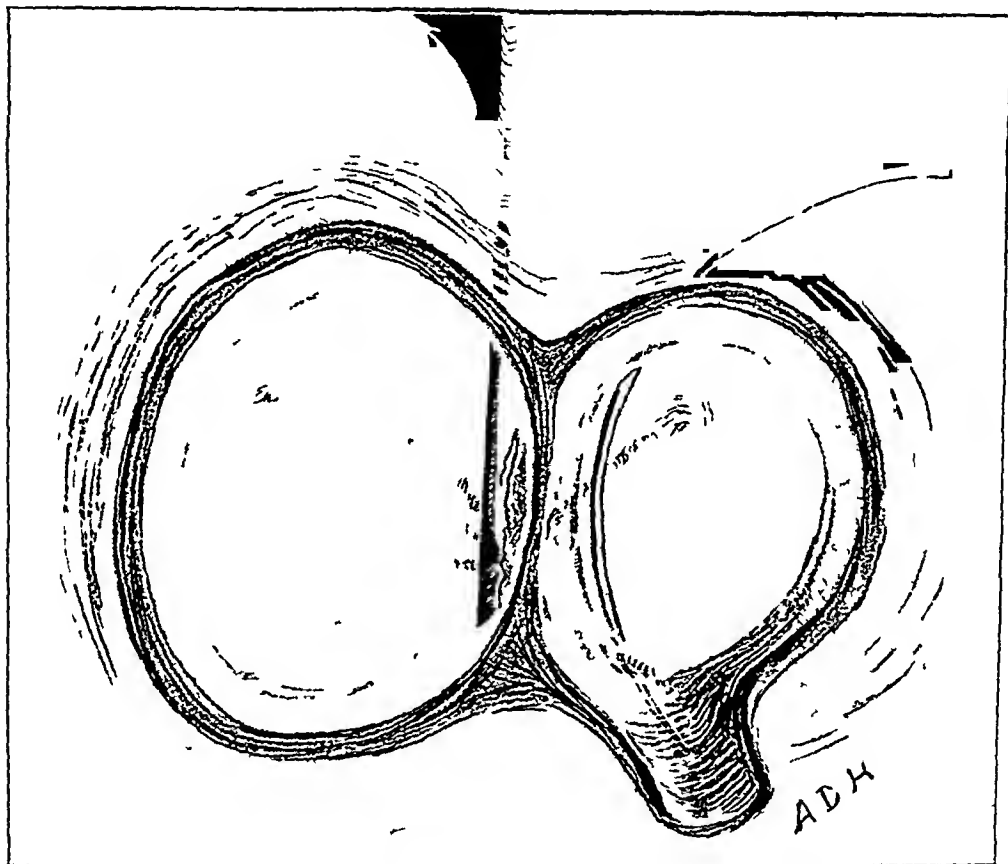
Fig 2 —The ventricles viewed from above showing the curved needle inserted
into the right ventricle and the knife blade cutting the bundle in the left   The
atrio ventricular bundle is shaded lighter than the rest of the heart muscle   The
arrow shows the direction in which the knife handle is moved to make the cut

We have found that curves bearing more or less resemblance to those
published by Professor Hewlett may sometimes occur when the apex-
beat disappears at the height of respiration, but Professor Hewlett has
assured one of us that this will not explain many of the tracings which
he has obtained

10 Hewlett A W   Heart Block in the Ventricular Walls THE ARCHIVES INT
MED Chicago 1908 ii 139

Schmoll,[11] in the same year, published an article entitled ' Ataxia of the Heart Muscle," in which he carried the idea of incoordination one step farther and voices Wenckebach's view that "not the whole ventricle is contracting, but only certain parts of it " This explanation seems thus far devoid of physiological basis MacCallum has shown that very large portions of the left ventricle can be thrown out of function by injection of alcohol into its substance without affecting the coordination of the chambers or even the blood pressure On the other hand the only definite experimental evidence of incoordination in the fibers of the ventricles is seen in the well-known phenomenon of fibrillary contractions during which the circulation absolutely ceases and the blood pressure invariably falls at once to zero Moreover, all of Schmoll's curves admit of interpretation in accordance with the well known types of phlebogram, without assuming an interventricular block
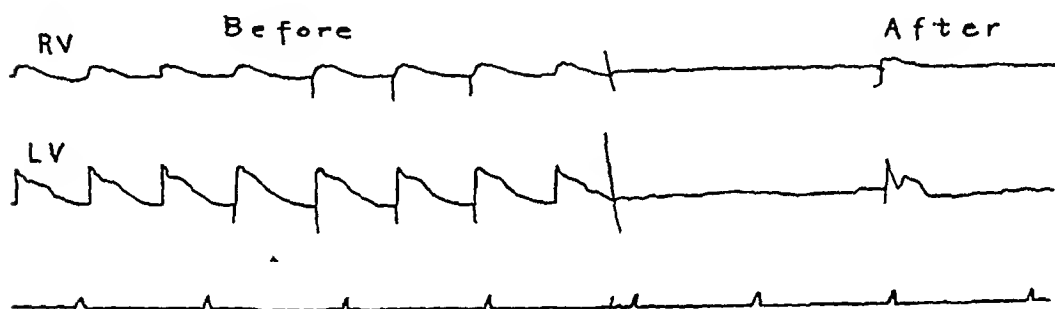
Fig 3 —Contractions of right (RV) and left (LV) ventricles recorded by the myocardiographs before and after cutting the left branch of the atrioventricular bundle Time in seconds

The subject of interventricular heart-block, therefore, seemed worthy of experimental investigation Several months prior to Hewlett's publication one of us had attempted to cut the left branch of the His bundle in the upper part of the ventricular system by introducing a knife through the wall of the ventricle and cutting into the septum, in the hope of blocking the cardiac impulse to the left ventricle but not to the right

The number of experiments tried was too small to be conclusive, but no such incoordination was produced During the past winter we attempted to carry on these experiments with an improved technic The contractions of the ventricles were recorded by means of two myocardiographs This apparatus (Fig 1) made according to the suggestion of Dr Dozier of San Francisco consisted of a double-ended tambour 2 5

11 Schmoll F   Ataxia of the Heart Muscle Am Jour Med Sc 1908, CXXXVI, 663

cm in diameter, armed with two wire levers   The lower arms of the levers (2 cm long) were hooked for insertion into the muscle of the ventricles, while the upper ends, above the fulcrum, were also 2 cm long and passed through holes in a celluloid foot which was glued to the dam of the tambour   A small (0 3 mm) brass tube led off from
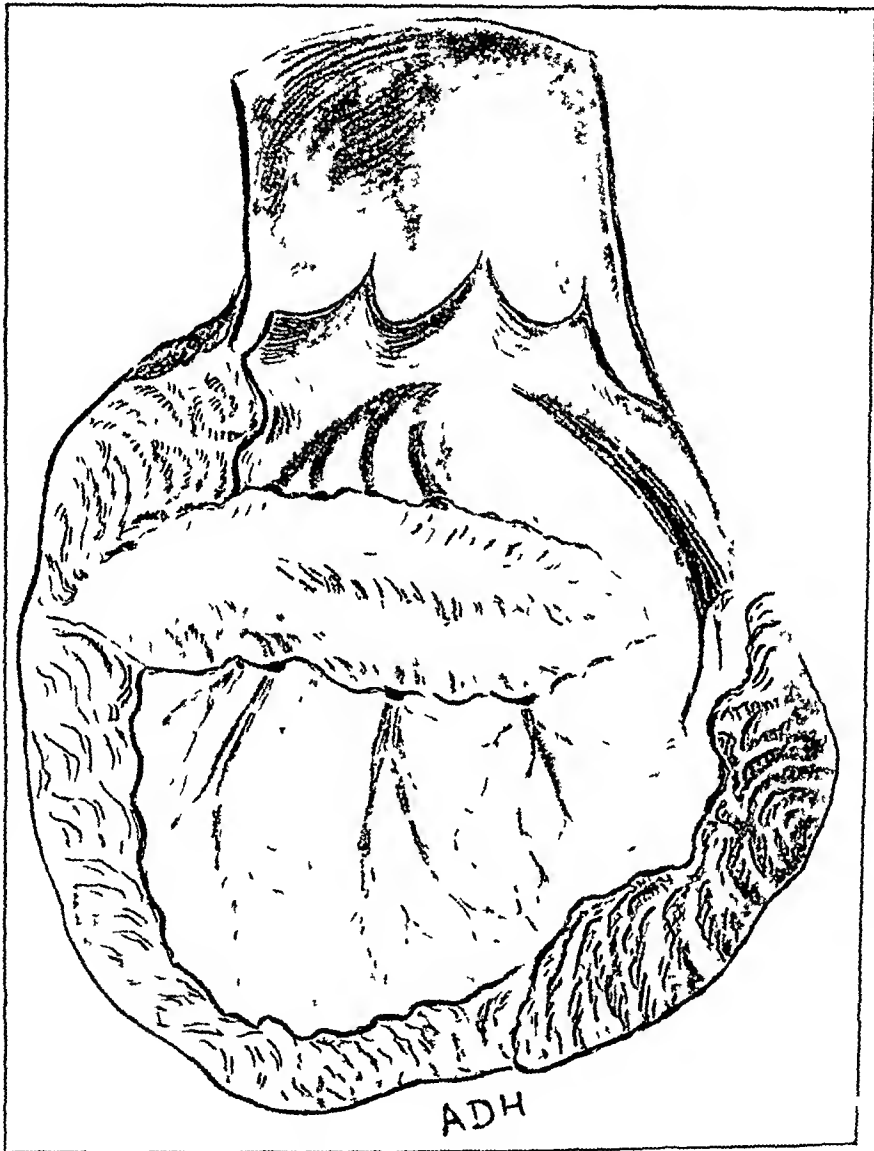
Fig 4 —The left ventricle showing the cut through all the ramifications of the left branch of the atrio ventricular bundle, which appear lighter than the rest of the heart muscle

the central myocardiograph tambour and was connected with the recording tambour by rubber tubing

In the earlier experiments we attempted to cut the left branch of the His bundle with a firm knife-blade run into the ventricle through the

carotid artery and aorta   (During its passage the knife-blade was pro-
tected by a cardiac sound, from which it was then extruded)   This
method was unsatisfactory, since it was difficult to do more than nick
the walls of the septum

A small knife-blade about 3 mm in width was then used, it was
introduced through the left wall of the ventricle as near as possible to
the mid-line, and the septum was cut by a drawing stroke, pressing the
handle of the knife to the left while drawing it toward the operator
In this way one successful operation was performed   However, after
many partial cuts had been made, in which the anterior and posterior
parts of the septum were nicked, but the middle portion of the septum
left uninjured, it became evident that the interventricular septum must
assume a concave form (with concavity toward the left) during sys-
tole   This was overcome by introducing a long curved needle into the
anterior wall of the right ventricle as near as possible to the septum
following along the septum to the posterior wall, and penetrating the
latter   The right ventricle was thus impaled on the curved needle and
the concavity of the left aspect of the septum converted into a con-
vexity (Fig 2)   When the knife-cut was now made as before it was
much more often successful

In all, fourteen operations were performed, in five of which the left
branch of the His bundle was cut without injury to the right

In all but one of the successful experiments this was followed by
complete atrioventricular heart-block, but both ventricles contracted
synchronously (Fig 3)   The rhythm was the slow, regular, independent
ventricle rhythm   In these experiments several cuts were made, and the
heart stopped beating after a few minutes, so that it can not be stated
whether the complete block was due to the section of the branch and the
trauma to the entire bundle, or was merely a terminal phenomenon

In one experiment, however in which only a single cut was made
the ventricular rate remained entirely unchanged and no block was
present   The heart continued to beat vigorously even after removal from
the body   The left branch of the Λ was cut through (Fig 4) but the
septum was not pierced and the right branch was absolutely intact
(Fig 5)

From the clinical and pathological side our experiments have the
further confirmation that Saigo[12] found fatty degenerations and patches
of myocarditis affecting the left branch of the bundle in many cases in

12 Saigo   Die Purkinjeschen Muskelfasern bei Erkrankungen des Myocards
Verhandl d deutsch path Gesellsch Jena 1908 XII 165

which the heart rate had been quite normal, and in which there had been no trace of ventricular incoordination

It would appear therefore, that the His bundle plays little if any rôle in the coordination of the two ventricles This might be expected
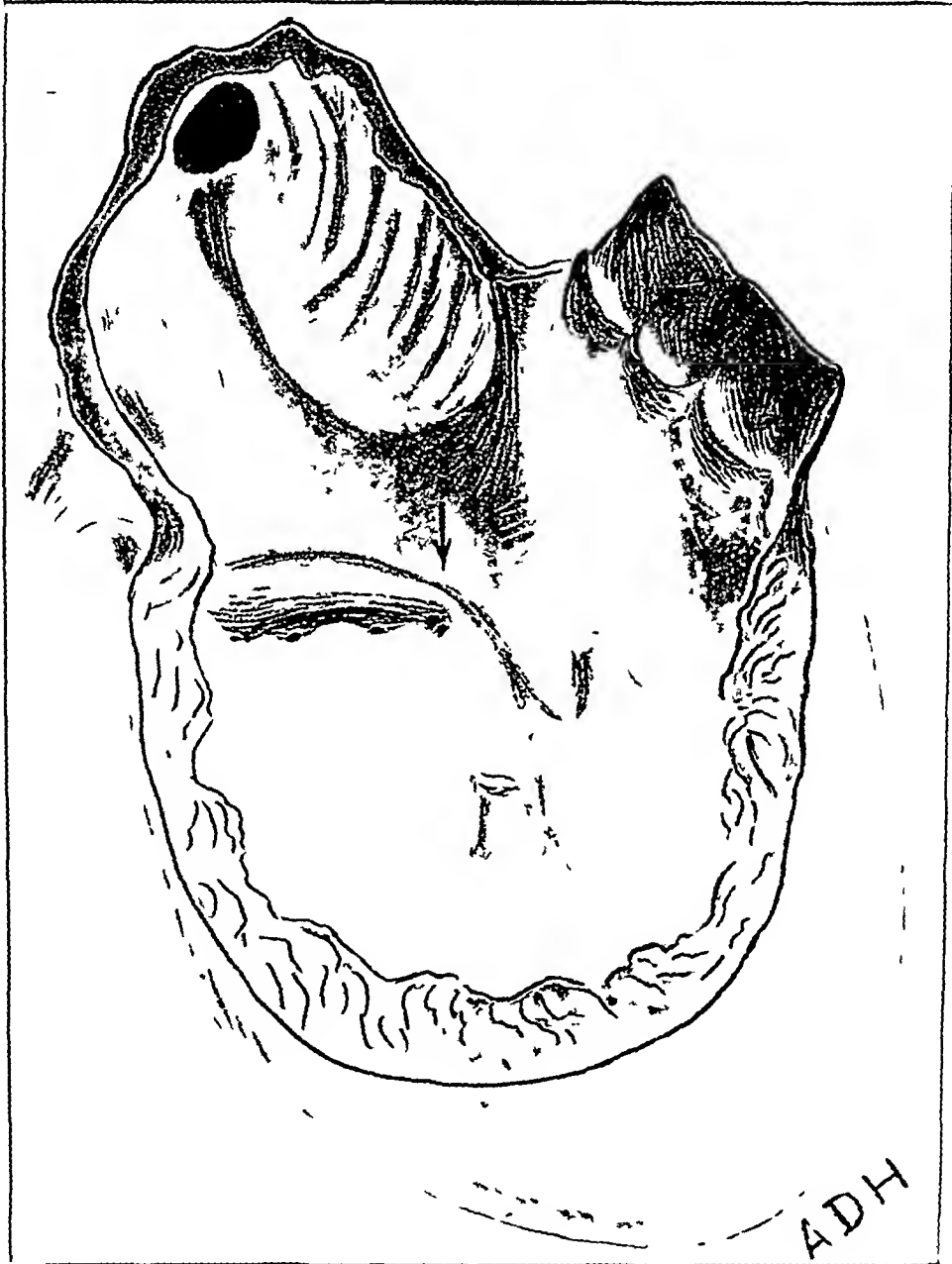
Fig 5 —The right ventricle of the same heart showing the septum and right branch of the atrioventricular bundle (indicated by the arrow) intact

since Ludwig Kiehl and MacCallum have shown that the fibers of one ventricle pass without interruption into those of the other The muscu-

lar bridge between the two chambers is formed by the entire muscula-
ture of the heart wall, and hence there is no such narrow connection
as is present between atria and ventricles at which a block might be pro
duced   It seems more probable that any such incoordination, if present
would be between the different layers of muscle fibers common to the
walls of both ventricles, rather than between the two ventricles them-
selves, and that in some cases of apparent hemisystole seen in animals
just before the heart stops beating (and after the circulation has ceased)
the outer layer of fibers in one ventricle has stopped beating, while the
outer layer of the other (inner layer of the first) continues to beat for
a few moments longer

It is not our intention to claim that no such thing as a hemisystole
ever occurs under clinical conditions, but merely that in the absence
of experimental evidence of its occurrence a considerable degree of skep-
ticism is warrantable   The experience of von Leyden demonstrates how
easily a false interpretation of these phenomena may be made when
founded on clinical observations alone

We take great pleasure in expressing our thanks to Drs George M
Bond and Elizabeth S Hellweg for their kind assistance in these experi-
ments

6 East Franklin Street—2243 Linden Avenue

EXPERIMENTAL PAROTITIS *

ISABELLA C HERB, M D
CHICAGO

The most noteworthy study of the bacteriology of mumps is by Laveran and Catrin,[1] who in 1893 described a diplococcus in the exudate which they obtained by aspiration of the parotid gland   They found this diplococcus 67 times in 92 cases, 39 times the organism was obtained in pure culture, twice in mixed culture and 15 times the result was negative   The 15 negative results they attribute to the small quantity of exudate obtained   In 16 cases of secondary orchitis pure culture was obtained 12 times, once with contamination and three times they obtained no growth   The organism was obtained from the blood during the height of the fever 10 times in 15 examinations   Three times pure cultures were obtained from the edema of the overlying tissue of the gland and once from the exudate of a joint   They found it fatal in large doses to white mice   Injections into the testicles of rabbits produced an inflammation which lasted about eight days

In 1896 Mecray and Walch[2] examined the saliva from Steno's duct in 10 cases   They found a diplococcus 6 times   In 8 blood examinations they obtained the organism in pure culture 3 times mixed with the white staphylococcus 3 times, and twice their results were negative   In the same year Busquet and Feri[3] examined the blood and saliva in 3 convalescents and in 17 patients during the early stages of the disease and found a diplococcus in all the cases

In 1897 Michaelis and Biem[4] examined the secretion from Steno's duct in 16 cases and obtained pure cultures of a diplococcus in all   Their animal experiments gave negative results

In 1906 Teissier and Esmein[5] examined the blood in 45 cases and obtained a diplococcus in 37   The negative results were in those with a light attack of the disease or during convalescence   The organism was

1 Laveran and Catrin   Compt rend soc de biol 1893 v, 528
2 Mecray and Walch   Med Rec 1896 i 440
3 Busquet and Feri   Rev d med 1896 xvi 744
4 Michaelis and Biem   Verhandl XV Cong f inn Med 1897 xv 441
5 Teissier and Esmein   Compt rend soc de biol 1906 lx 803 853 897

obtained 33 times in pure culture, twice with streptococci, twice with a
bacillus and three times with a coccobacillus   The exudate from Steno s
duct showed in 10 examinations 9 pure cultures   The coccus was fatal
to guinea-pigs and rabbits   Following intraperitoneal inoculations an
orchitis developed in 4 of 7 rabbits

In 1907 Korentschewsky[6] isolated a diplococcus from the gland
exudate in 21 of 29 cases   His blood examinations gave positive results
in 8 of 32 cases   The organism was fatal to mice, guinea-pigs and rab-
bits in large doses   No results were obtained in dogs

So far as may be judged from the description of the investigators
I have cited it appears very probable that they have dealt with the
same diplococcus
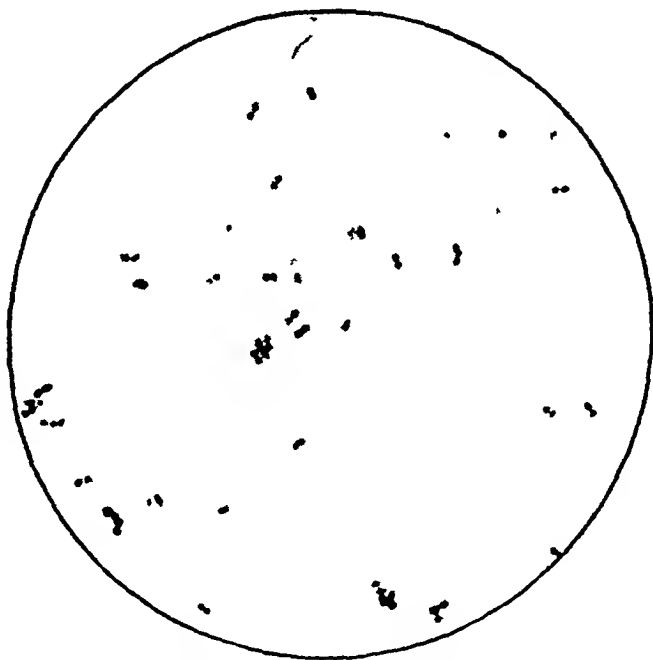
Fig 1 —Smear from thirty six hour old growth on glycerin agar　× 1200

SOURCE AND DESCRIPTION OF DIPLOCOCCUS USED IN THE EXPERIMENTS

A similar diplococcus was obtained by me from the body of a man
about 40 years old who entered the hospital in a moribund condition
and died in a few hours   Except the report that he had had mumps
no history was obtained   The postmortem by Dr LeCount showed a
right suppurative parotitis, bronchopneumonia and several minor
lesions

The cerebrospinal pleural and pericardial fluids bile spleen, lung,
testicle and right parotid gland were examined bacteriologically   Cover-

6 Korentschewsky   Centralbl f Bakteriol, 1907, xliv, 394

glass pieparations from the bile, pericardial and cerebrospinal fluids showed a rather large diplococcus, the latter also contained a small coccus occurring in groups   The pleural fluid contained a short bacillus   They were both Gram-positive   *Proteus vulgaris* was isolated from the pleural, cerebrospinal and pericardial fluids, the spleen, lung, testicle and parotid gland, *Staphylococcus albus* from the lung, testicle, cerebrospinal fluid and parotid gland   From the lung, testicle, cerebrospinal and pericardial fluids, bile and parotid gland a coccus was isolated with the following characteristics

The coccus appears most frequently as a diplococcus, occasionally in chains of 4 to 6 elements, or in small groups (Fig 1)   It is round and

Fig 2 —Uniform enlargement of the left parotid gland of dog on fourth day after injection of diplococcus into Steno's duct

measures from 0 5 to 0 8 microns when about twenty-four hours old When several days old it measures from 0 6 to 1 5 microns   It is easily stained by all the ordinary anilin dyes and is Gram-positive   It grows equally well aerobically and anaerobically   It is not motile has no capsule or flagella and does not form spores gas or indol   It grows best at 37 C   50 C for three minutes destroys growth   cold inhibits but does not prevent growth when the culture is again placed under favorable conditions   Colonies developed from a milk culture two months old

and from agar which was dried till it was broken   While the coccus develops on all the ordinary media, its growth is characteristically slow, the twenty-four-hour glycerin agar colonies being scarcely visible

Saliva being the natural secretion of the parotid gland, it was thought that the organism would grow more luxuriantly on a medium in which saliva was incorporated   This was found to be true, an abundant growth being obtained in half the time required on other media Saliva was collected in test-tubes and passed through a porcelain filter (Pasteur-Chamberland)   Nutrient agar-agar was heated to the melting point, allowed to cool to 48 C, and about ten drops of the sterile saliva added to an ordinary agar tube   The tube was then rapidly rolled between the hands in order to mix the agar and saliva

Fig 3 —Showing parotid of same dog as represented in Figure 2, killed by chloroform on the fourth day after injection, skin and muscles have been removed

thoroughly and solidified in the oblique position   The tubes were now incubated at 37 C for forty-eight hours and carefully examined with a lens to make sure they were sterile before inoculating them   Sufficient saliva should be added to form some fluid of condensation

Ascitic agar is also better medium than glycerin agar, but not so good as the saliva agar

Glycerin Agar Stroke —Pearly white, pin-point, discrete colonies without pigment

Saliva Agar and Ascitic Agar Stroke —Similar to glycerin agar but earlier and more abundant growth

Human Blood Agar —Pin-point, round, discrete colonies, surrounded by a clear white zone of hemolysis

Blood Serum, Loeffler's —Firm, white beaded growth without liquefaction of the medium or formation of pigment

Potato —Dull grayish-white, scanty growth without pigment

Agar Stab —Delicate beaded growth along line of puncture

Glucose Agar —Similar to plain agar No gas

Litmus Milk —Soured in twenty-four hours, coagulated in forty-eight hours

Plain Broth —Slight clouding in twenty-four hours, later an abundant tenacious growth in the bottom of the tube .
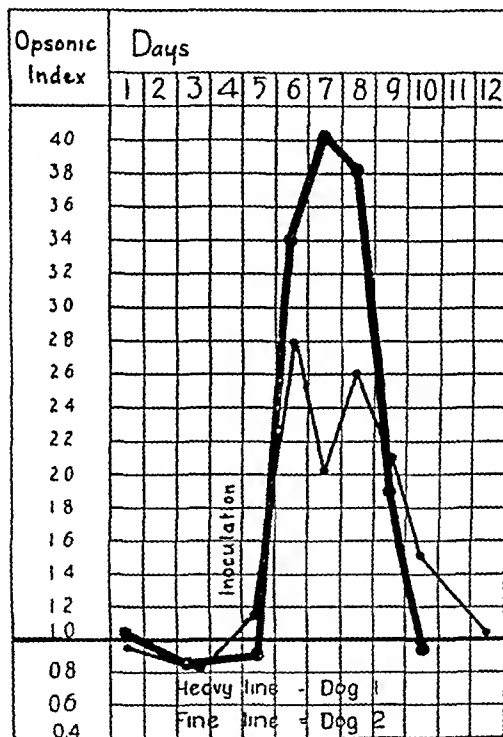
Fig 4 —Chart of opsonic index in experimental mumps of dogs (For history of Dog 1 see Experiment 2 The history of Dog 2 is not given)

Gelatin —Beaded growth along line of inoculation appearing about the third or fourth day with liquefaction of the medium in four or five weeks

EXPERIMENTS

The organism is fatal to white mice, white rats guinea-pigs and rabbits when injected subcutaneously or intraperitoneally In the latter case the animals usually die within twenty-four hours of peritonitis Those that survive for several days die of bacteremia The growth

from a forty-eight hour agar slant suspended in 1 c c normal salt solution injected into the testis of rabbits produces an acute inflammatory condition which lasts for seven to ten days and then disappears without suppuration, the structure later appearing perfectly normal   On the other hand, animals similarly inoculated with staphylococcus or streptococcus die of peritonitis within twenty hours, while an injection of normal salt solution alone produces no reaction
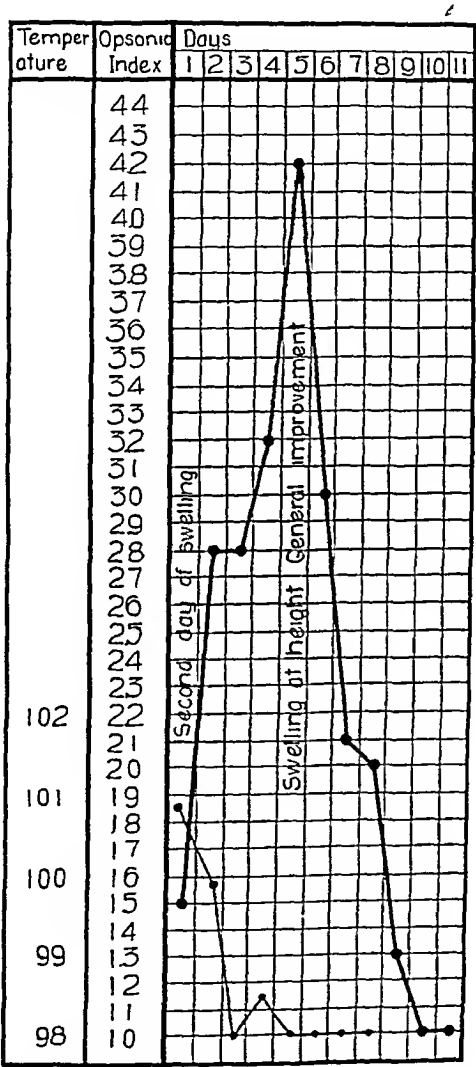
Fig 5 —Chart of opsonic index for the diplococcus studied in a case of mumps

The following experiment was made on a medium-sized so-called white-faced ringtail monkey

Experiment 1—On February 7 the animal (temperature 100 8 F) was inoculated through the right Steno's duct with the growth from a forty eight hour ascitic agar slant suspended in 1 c c normal salt solution

February 8   Temperature 103 F   slight swelling of the parotid, refuses food

February 9   Temperature, 103 2 F, decided enlargement of the parotid chews with difficulty, but does not appear sick

February 10   Temperature 101 8 F, parotid about as yesterday, less difficulty in chewing, appetite good

February 11   Temperature, 101 2 F   parotid smaller than yesterday

February 12   Temperature, 100 8 F, swelling of the parotid gradually disappearing
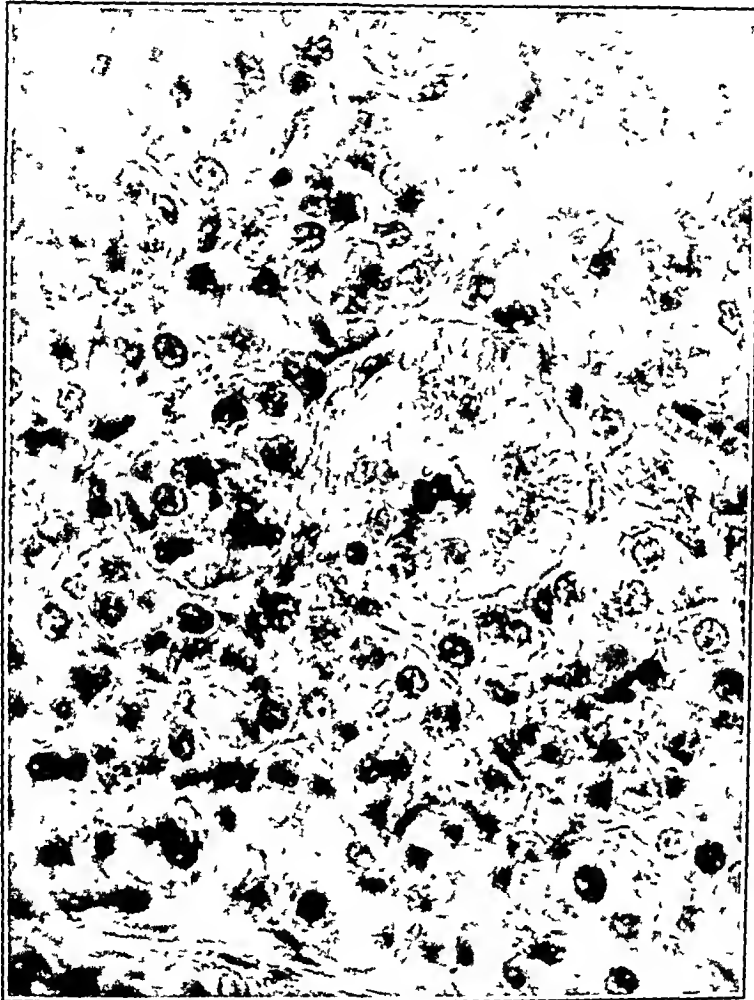
Fig 6 —Section of the parotid of dog on second day after injection of the diplococcus into Steno s duct   × 650

February 13   Temperature, 100 2 F   swelling of parotid gradually disappearing

February 14   Temperature 100 2 F   parotid appears of normal size

Most of my experiments have been on dogs   In passing it may be noted that Busquet and Boudeaud[7] record an instance of mumps in the

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7 Comp rend soc de biol lii 675

dog, a second animal getting the disease from the first They isolated
a "diplostreptococcus" from the saliva in Steno's duct in both dogs and
from the blood of the second

The dog seems to react in a characteristic manner to the intro-
duction of the coccus I have studied into the parotid gland, while sub-
cutaneous and intraperitoneal inoculations produce no results Direct
inoculation into the parotid gland of dogs causes a swelling of the
gland, lasting for seven to ten days The injection of suspensions into
Steno's duct produces in dogs a uniform swelling of the parotid gland

Fig 7 —Section of the parotid on fifth day after injection   × 650

which begins in from 48 to 72 hours, continuing to enlarge for
a few days, when the gland gradually returns to normal size
In these animals the temperaure during the period of the swell-
ing of the gland ranges from 1 to 1 5 F above normal, in no case did
suppuration develop and with the exception of difficulty in chewing
for a day or two the animals appear to suffer no special inconvenience
(Figs 2 and 3)

Injections into the duct of mixed cultures of the organism and staphylococcus causes edema of that side of the face and the parotid gland in three or four hours and abscesses form in three or four days In two dogs that survived these injections after drainage of the abscesses the parotid gland was completely destroyed One dog died on the fifth day of bacteriemia, another developed lung abscesses and died on the twenty-third day
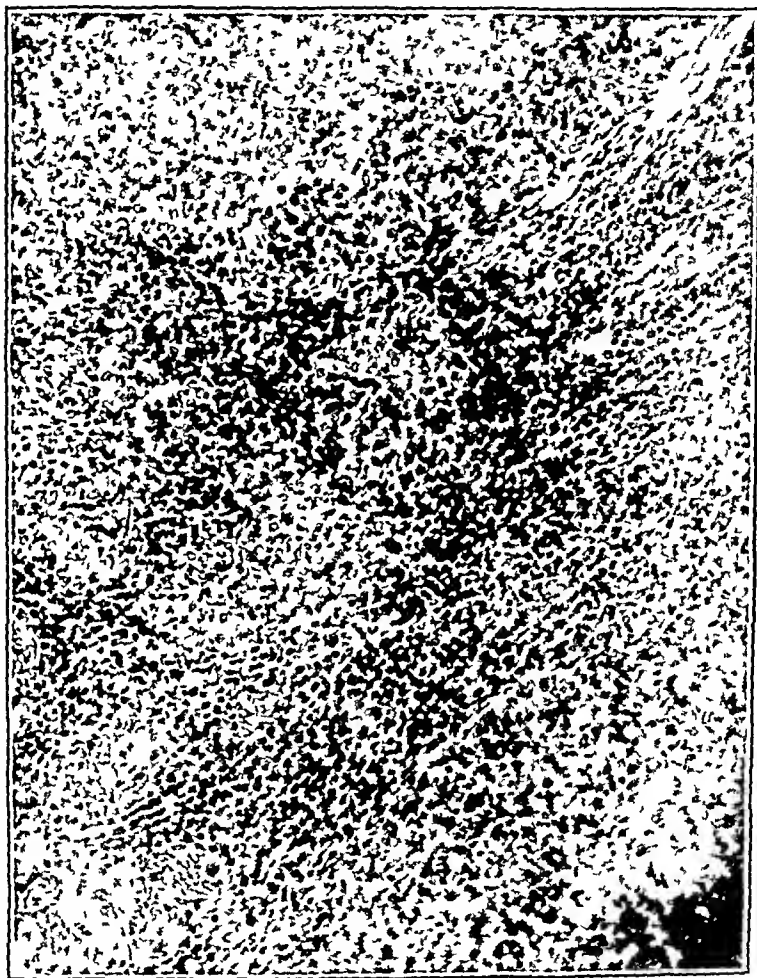
Fig 8—Section of the parotid on sixth day after injection × 150

The following records of experimental inoculations of the diplococcus into Steno's duct in the dog illustrates well the changes thus produced in this animal

Experiment 2 (Dog 1) —February 24 Small young black and white dog Temperature 102 5 F Inoculated into the left Steno s duet with the bacteria from two forty-eight hour saliva agar slants suspended in 3 c c broth

February 25 Temperature 102 5 F No visible change

February 26 Temperature 103 F Parotid enlarged Dog whines when firm pressure is made over the gland

February 27   Temperature, 103 5 F   Parotid evenly enlarged and hard   Dog does not act ill, is playful and hungry, but experiences difficulty in chewing

February 28   Temperature, 102 8 F   Gland about as it was yesterday   Pure cultures of the organism injected developed from aspirated fluid

March 2   Temperature, 102 5 F   Swelling gradually disappearing

March 5   Temperature 102 5 F   Almost no enlargement of the gland

March 6   Temperature, 102 5 F   Gland appears normal

For the opsonic index see chart (Fig 4), heavy line

Experiment 3 (Dog 7) —April 21   Large fox terrier (temperature 102 F) was inoculated through the right Steno's duct with a forty-eight hour growth from three tubes suspended in broth   Leucocyte count, 12,350
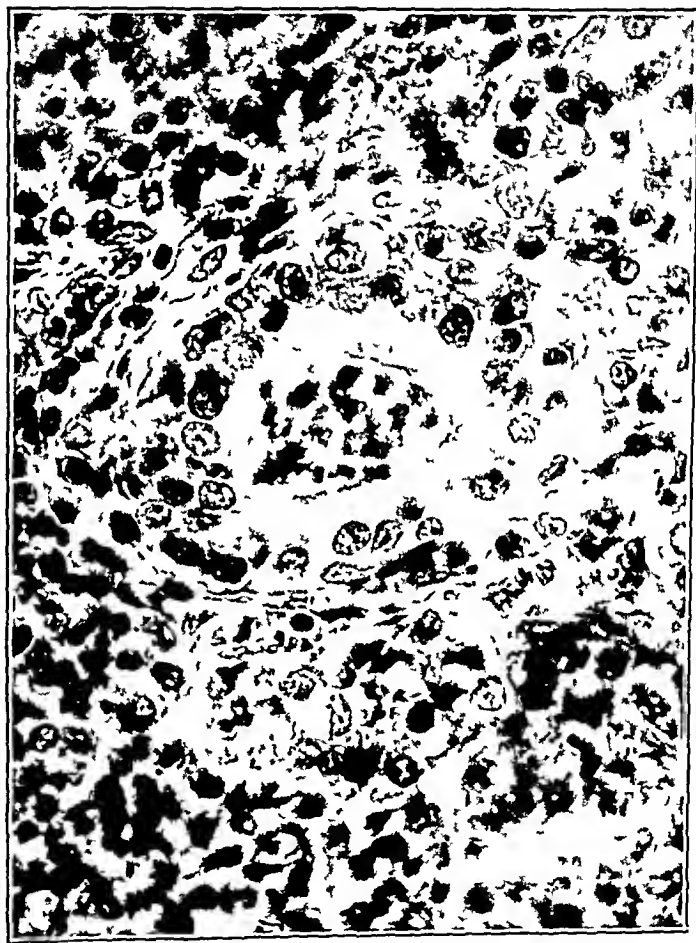
Fig 9 —Section of the parotid on sixth day after injection   × 650

April 22   Temperature, 103 F   Dog appears well   Leucocyte count, 12,350   Opsonic Index, 1 6

April 23   Temperature 102 F   Dog shows swelling of parotid   Some difficulty in chewing   Leucocyte count, 31 200   Opsonic index 1 2

April 24   Temperature 102   Parotid considerably larger than yesterday   Dog whines when pressure is made over gland   Difficulty in chewing   Testicles appear firmer and larger than normal   Leucocyte count 31,000   Opsonic index 2 2

April 25   Tempeiatuie, 102 F   Paiotid evenly enlaiged and haid   Dog ap
pears well and eats with less difficulty   Testicles about as they weie yesteiday
Leucocyte count, 30,000   Opsonic index, 2

April 27   Tempeiatuie, 1014 F   Paiotid slightly decieased in size   Leu-
cocyte count, 20,600   Opsonic index, 2 4

April 28   Tempeiatuie, 1018 F   Paiotid smallei than yesteiday   Leucocyte
count, 23,700   Opsonic index, 1 9

April 28   Tempeiature, 1018 F   Paiotid smallei than yesteiday   Leucocyte
count, 23,700   Opsonic index, 1 9

April 29   Tempeiature, 1025 F   Swelling of paiotid iapidly disappearing
Leucocyte count, 10,400   Opsonic index, 1 4

April 30   Tempeiatuie, 1018 F   Paiotid almost noimal in size   Leucocyte
count, 12,800   Opsonic index, 1

Fig 10 —Section of the parotid on sixth day aftei injection   × 1250

Unfoitunately no diffeiential leucocyte counts weie made in this
case   In othei moculated animals in which counts weie made the same
leucocytosis was obseived and found to depend apparently on a uni-
foim inciease in the difieient forms of leucocytes   Sacquépée[8] found
a modeiate leucocytosis due to inciease in the mononucleais in oidinaiy
mumps without oichitis, while F Pick[9] did not find any leucocytosis in
mumps, but a ielative inciease in the mononucleais and a ielative de-
ciease in the polymoiphonucleais

8 Sacquépée   Arch de méd expéi et d anat path 1902 ix 114
9 Pick, F   Wien klin Wehnschi 1902 xvi 309

Negative results weie obtamed in dogs inoculated thiough Steno's duct with filtiates of old bioth cultures and suspensions of the diplococcus heated to 60 C for 30 minutes The opsonic index did not seem to be affected by these inoculations

OPSONIC INDEX IN A CASE OF MUMPS

In spite of many effoits to secuie opportunity to study cases of mumps during the progress of this investigation only one suitable case came under observation The opsonic index of the serum of this patient foi che diplococcus described in this report shows a well-maiked iise at the peiiod of the height of the swelling just as the tempeiatuie was retuining to noimal (Fig 5) The clinical iecord follows
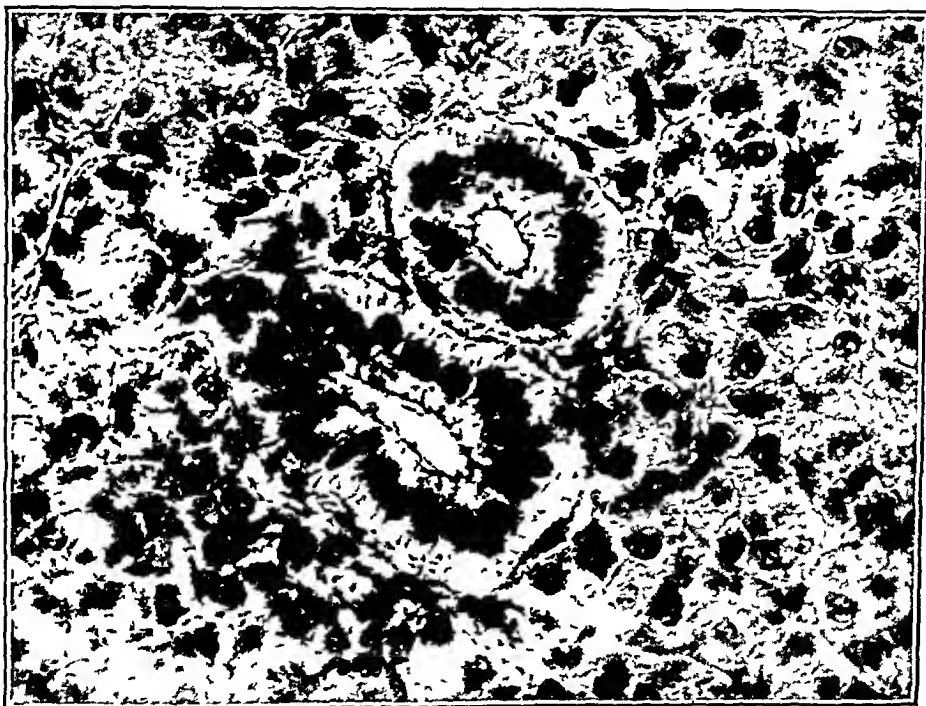
Fig 11 —Section of paiotid on tenth day aftei injection Complete iestitution × 650

Woman aged 23, tiamed nurse, was caring for a child with mumps when she noticed (Septembei 24) a swelling of the left side of the face

Septembei 25 Tempeiatuie 100 F Swelling has meieased and patient feels geneially uncomfoitable, has sevee headache and difficulty in chewing

Septembei 26 Tempeiatuie 99 F Swelling of paiotid and iegional lymph glands quite maiked Head still aching, no appetite

Septembei 27 Tempeiature 98 F Paiotid and iegional lymph glands much enliiged and veiy haid Some discomfoit is felt when fiim piessuie is made ovei the paiotid

Septembei 28 Tempeiatuie 98 F Is feeling better but no change in the swelling

September 29   Temperature 97 6 F   No change in swelling

September 30   Temperature, 98 F   Swelling seems less than yesterday Feels well and is hungry

October 1   Temperature, 98 F   Parotid and regional lymph glands decreasing in size

October 2   Temperature, 98 F   Feels well   Swelling decreasing

October 3   Temperature, 98 F   Swelling rapidly disappearing

October 4   Temperature 98 F   Swelling almost gone   Patient feels perfectly well

GROSS AND MICROSCOPIC ANATOMY OF EXPERIMENTAL MUMPS IN DOGS

The enlarged parotid of inoculated dogs is of uniform firm consistency, the enlargement often reaching many times the normal size (Figs

Fig 12 — Section of cervical lymph of dog on seventh day after injection of the diplococcus into Steno's duct   × 150

2 and 3) the cut surface is pinkish exuding a little pinkish, rather turbid, fluid The neighboring lymph nodes are moderately swollen but there are no gross changes in other parts of the body

Dogs inoculated through one or both Steno's ducts were chloroformed at various stages of the disease and sections made of the internal organs and bone marrow for microscopical study In others the process was not disturbed and in these the blood changes were studied

Pieces of tissue for microscopic study were removed immediately after the animals were killed and placed either in 85 per cent alcohol

or Orth's fluid Sections fixed in alcohol were embedded in paraffin, while those fixed in Orth's fluid were embedded in celloidin after being washed in running water for twenty-four hours The femur was selected for the study of the marrow The bone was sawed lengthwise and placed in alcohol When the marrow was sufficiently fixed it was removed and embedded in paraffin The marrow was stained with polychrome methylene blue and eosin, all the other tissues in hematoxylin and eosin

Fig 13 —Section of the testis of a dog on fourth day after injection of the diplococcus into Steno's duct Cellular interstitial infiltration × 150

On the second or third day after inoculation there is a diffuse cellular infiltration of the interstitial tissue of the parotid which extended to the interlobular tissue to a slight extent At the height of the swelling of the gland the cellular invasion has extended to the acini The cells lining the ducts are swollen occasionally desquamated, the lumen packed with cells and cell detritus The ducts are the last to become

involved and the first to recover   The invading cells are composed of
large polygonal cells with a vesicular nucleus, many containing small
dark chromatin granules or nuclear fragments, plasma cells, and a few
lymphocytes and degenerated cells   By the end of the second week the
gland has returned to normal condition   Suppuration or necrosis never
occurred (Figs 6-10)

The cervical and posttracheal lymph nodes show an early involve-
ment   The capsule and trabeculæ contain distended vessels and there is
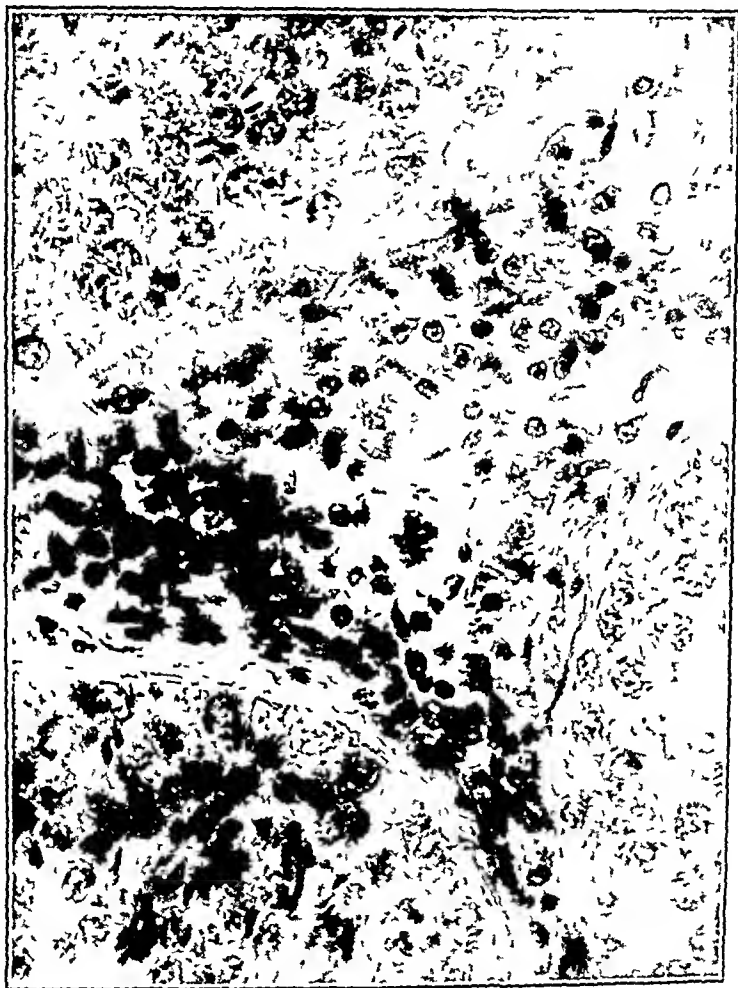
Fig 14 —Section of testis illustrated by Fig 13 at higher magnification
× 500

more or less cellular infiltration   The lymph spaces are widened and
filled with cells and the outline of the secondary follicles and medullary
cords are indistinct (Fig 12)   In all the sections examined the cortical
lymph nodes as a rule are difficult to define   The sinuses contain nu-
merous large polygonal or elongated cells with a large vesicular nucleus
or a large round nucleus with deeply staining chromatin granules

increase in number of lymphocytes, phagocytic cells with two or more partly digested cells as also red blood cells and blood pigment

In the sections of spleen examined the capillaries are distended with blood and there is increase in the large, round, granular mononuclear cells, leucocytes and small lymphocytes, nucleated red cells and large, marrow giant cells In the spleen of one dog killed five days after inoculation there is a very marked increase in the nucleated red cells, which appear in clusters or groups of six or more The follicles are swollen and contain numerous large polygonal cells with a vesicular nucleus

In the bone marrow, so far as the comparatively few sections examined permit any statements, changes appear about the time the parotid begins to enlarge, but they disappear somewhat earlier than the parotid swelling subsides There is a noticeable increase in the mononuclear cells, particularly in the neutrophilic myelocytes and the undifferentiated lymphocytes of Wolf, and also in the nucleated red cells Slight increase in the megakaryocytes, eosinophiles and polymorphonuclear cells These changes are most pronounced during the height of the infection

An orchitis was present in one of the three male animals killed for microscopic examination It is thought that this condition was present in some of the animals that recovered, as the glands appeared somewhat enlarged and firmer than normal From a careful study of the material at hand (Figs 13 and 14) it seems that the inflammation begins as a cellular infiltration in the intestinal tissue and soon invades the tubules The cells forming the infiltration are of the mononuclear variety, the majority being polygonal cells with an eccentrically placed nucleus and a large amount of protoplasm, there are also cells with a uniformly densely staining eccentric nucleus, cells with a large vesicular nucleus and a small rim of protoplasm About the time the invading cells penetrate the walls of the tubuli contorti there occurs a swelling and more or less indistinctness of the Sartoli and spermatogenic cells, with a cessation of mitosis in the spermatogenic cells The spermatoids appear unaffected by the process Unaltered spermatozoa are found in all the tubules except those most profoundly affected, in which they are absent The cells lining the tubuli recti are swollen and the lumen is filled with desquamated cells and cell detritus No areas of suppuration or necrosis were observed The inflammatory changes consequently correspond to those which occur in the parotid

About the time the parotid becomes enlarged the tubular epithelium of the kidney becomes swollen, cloudy, fatty and occasionally *desqua-*

mated The lumen is more or less filled with granular material Later
there is an intense engorgement of the blood channels extending into
the peripheral zones, about the fourth or fifth day after inoculation,
cells are occasionally seen

The pancreas, lung and suprarenals present no changes worthy of
note

The liver shows a slight cloudy swelling, with deposition of fat in
the peripheral zones, about the fourth or fifth day after inoculation,
later there is a marked congestion of the central and interlobular veins
so that the liver cells are pressed into narrow bands Small groups of
mononuclear cells are present in the majority of sections

SUMMARY

The principal, distinguishing or characteristic features of the diplococcus isolated from a case of mumps are the following

Gelatin is very slowly liquefied In broth a slight cloudiness is produced in twenty-four hours, later a tenacious deposit forms in the bottom of the tubes Milk is soured in twenty-four hours and coagulated in forty-eight hours Potato produces a grayish-white abundant growth On blood agar a slight zone of hemolysis appears around the colonies Agar cultures show pearly white, tenacious, pin-point, round, discrete colonies No production of indol The organism occurs most frequently as a diplococcus, occasionally in small groups or chains of from four to six elements It is non-pyogenic

When injected into Steno's duct in monkeys and dogs this diplococcus causes a diffuse non-suppurative parotitis, the infiltration being composed largely of mononuclear cells, and occasionally also orchitis of a similar character During the course of this experimental parotitis the opsonic index for the diplococcus shows a marked rise reaching the highest point at about the time when the parotid swelling is most marked In one case of human mumps (the only one studied) a similar rise of the opsonic index for this organism took place There is consequently good reason to regard this diplococcus which corresponds well with the description given by Laveran and Catrin of the diplococcus isolated by them from cases of mumps, as the actual cause of mumps and the disease produced in my dogs as genuine experimental mumps

CERTAIN UNUSUAL LESIONS OF THE LYMPHATIC APPARATUS

INCLUDING A DESCRIPTION OF PRIMARY HODGKIN'S DISEASE OF THE SPLEEN AND A CASE OF GASTROINTESTINAL PSEUDOLEUKEMIA

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In 1832 Hodgkin[1] called attention to the existence of a disease characterized primarily by progressive enlargement of the lymph nodes and associated, in many instances, with enlargement of the spleen. In the light of our present knowledge it appears that several of the cases originally described by Hodgkin were examples of leukemia or of glandular syphilis or tuberculosis, but that at least two were genuine instances of the affection to which Wilks,[2] in 1856, gave the name of Hodgkin's disease and for which, in recent years, a definite histology has been established. Since the appearance of Wilks's paper in England, and a communication by Bonfils in France in the same year, many contributions have been made to the literature of the subject, and undoubtedly several different lesions have been described under the title of "Hodgkin's disease", among them leukemia, non-caseous glandular tuberculosis, lymphosarcoma and pseudoleukemia. Despite the confusion occasioned by lack of knowledge of the pathologic histology of Hodgkin's disease, the older observers came to recognize two types, and to regard them as different varieties of the same lesion—one soft and characterized by great cellular richness, the other firm and tending to become sclerotic. Indeed, in the latter type, giant cells were observed by Virchow in 1864 and by Langhans in 1872. Perhaps the first important step in the elucidation of a problem which is still beset by many difficulties was accomplished by Virchow when he established the independence of leukemia. Shortly thereafter a further advance was made by Cohnheim,[3] who, under the title of pseudoleukemia,[4] described a case which

1 Hodgkin. Med Chir Tr, 1832 xvii, 68

2 Wilks. Guy's Hosp Rep 1856, ii 1865 xi 56

3 Cohnheim. Virchow's Arch f path Anat, 1865 xxxiii 451

4 Cohnheim has been credited with the introduction of the term pseudoleukemia as a synonym for Hodgkin's disease but as a matter of fact he employed it to describe a totally different affection and in his original contribution did not once mention Hodgkin's disease or otherwise add to the confusion of the subject

presented the essential anatomical characteristics of leukemia without changes in the blood Gradually other lesions were eliminated from the general category of Hodgkin's disease and were more properly classified elsewhere, so that in late years Hodgkin's disease appears to have been recognized as a definite histological entity, characterized by changes which resemble those of the infective granulomata When fully developed these changes consist in proliferation of endothelial and reticular cells, the formation of giant cells, and progressive fibrosis, associated with variable numbers of lymphocytes and, in many instances at least, with plasma cells and eosinophiles, and were ably described by Steinberg[5] in a paper published under the title of "A Peculiar Form of Tuberculosis of the Lymphatic System" Other students of the disease have subscribed to the view that these changes are tuberculous or that they partake of the nature of tuberculosis[6] Still others have denied the etiological relationship of the tubercle bacillus to Hodgkin's disease, partly because of negative results following the inoculation of animals and the administration of tuberculin in the living subject, and partly because of repeated failures to demonstrate the tubercle bacillus in microscopical preparations of the organs involved

Practically all writers on the subject of Hodgkin's disease unite in declaring that the process almost invariably commences in the cervical or in anatomically related lymph nodes Reed[7] even goes so far as to state that "we know of no case where the pathological anatomy was described in sufficient detail to permit of a positive diagnosis, in which the disease commenced elsewhere" Lyon,[8] in Osler's "Modern Medicine" states that there is no evidence that a primary splenic form of Hodgkin's disease exists Simmons,[9] on the other hand, reports two cases of Hodgkin's disease that apparently commenced in the retroperitoneal lymph nodes, although no specific statement to this effect is made In both instances enlarged nodes were present in the neck In one case 'a few small discrete glands were found in the posterior cervical triangle on both sides" while the retroperitoneal nodes formed a mass about 16 cm in length and 7 cm in diameter In a second case there was a "discrete freely movable gland in the right posterior cervical triangle

5 Steinberg Centralbl f der Grenzgeb d Med u Chir 1899, ii 641 711, 770 813, 847

6 Ferran and Commotti Wien klin Rundschan 1900 xiv 1035 Crowder New York Med Jour 1900 lxxii 445 See discussion of Longcope's paper by Pearce and Ewing Tr New York Path Soc 1908 viii 133

7 Reed Johns Hopkins Hosp Rep 1902 x 133

8 Lyon Osler's Modern Medicine ed 1 Phila Lea & Febiger 765

9 Simmons Jour Med Research 1903 ix 378

just above the clavicle, the size of a hen's egg," and several smaller ones on the opposite side There were numbers of enlarged nodes in the abdomen, ranging in size from 2 to 7 cm In the latter case, however, we are left in some doubt concerning the primary focus of the disease, since neither the clinical history nor the autopsy protocol is sufficiently specific to dispel the suspicion that the cervical involvement was primary Longcope,[10] however has adequately described a case of Hodgkin's disease that originated in the retroperitoneal lymph nodes The patient was an emaciated man, 34 years of age, who, during life, presented signs of enlargement of the spleen and a moderate degree of anemia, together with elevation of temperature There were no enlarged nodes in the neck The skin and sclerae were jaundiced At autopsy the retroperitoneal lymph nodes were enlarged and the common bile duct was surrounded and compressed by nodular masses lying just below the entrance of the cystic duct

In the present communication I shall present the clinical and anatomical details of three cases of primary abdominal Hodgkin's disease one originating in the spleen, the other two commencing in the retroperitoneal lymph nodes At the same time I purpose to describe a remarkable case of pseudoleukemia in which practically the entire lymphoid apparatus, including that of the gastrointestinal tract, revealed the lesions of a generalized lymphomatosis and, in this connection, to emphasize the distinction between pseudoleukemia and Hodgkin's disease

HODGKIN'S DISEASE

CASE 1 —Primary Hodgkin s disease of the spleen M V, aged 18, single, corset maker, Belgian Admitted to the New York Hospital, June 1, 1908, died June 30, 1908

History—The patient stated that three years before admission to the hospital she had passed several blood clots per rectum At about the same time she observed that there was a mass in the abdomen For two or three years previously, however, she had noted that the circumference of her waist was increasing Four months before entering the hospital she began to experience irregularly recurring chills alternating with fever, sometimes two or three times in the course of a day Lately the ingestion of food has frequently been followed by vomiting, attended by generalized abdominal pains She never noticed the presence of blood in the vomited matter During the month that the patient was under observation the evening temperature rose on several occasions to 100 F or 101 F

Blood Count—
    Red cells, 4,684,000
    White cells, 7,000
    Color index 0 74

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10 Longcope Bull Ayer Clin Lab Pennsylvania Hosp, 1903, 1 4

Differential Leucocyte Count—

Polynuclear leucocytes, 85 per cent

Small lymphocytes, 11 per cent

Large lymphocytes, 4 per cent

No malarial organisms were detected in the patient's blood

Physical examination revealed a well-nourished woman The area of splenic dulness extended from the seventh rib on the left side to a point three inches below the umbilicus The edge of the organ was palpable 1 inch above Poupart's ligament on the left side whence it could be traced upward and to the right 2½ inches beyond the umbilicus, thence directly upward to the ensiform cartilage The superficial lymph nodes were not enlarged

On June 29 Dr Hartley removed the spleen through a vertical incision in the left rectus muscle The patient died the following day At the operation no enlarged abdominal nodes were observed No autopsy was obtained

Anatomical Description —The specimen consisted of a spleen 25 cm in length, 18 cm in breadth and about 8 cm in thickness The shape of the organ was well preserved The capsule was diffusely, but moderately, thickened and the surface presented a diffusely grayish-red color On section, the consistence of the organ was considerably increased and yielded a fine grating sensation when crushed between the fingers The substance of the spleen was grayish-red in color and scattered through it were innumerable minute connective tissue strands The Malpighian bodies were not visible The cut ends of the vessels appeared to be thickened

Two c c of an emulsion of the spleen in sterile bouillon were injected into the peritoneal cavity of a guinea-pig with negative results

Microscopical Examination —The lymphoid follicles were exceedingly few in number, not very rich in cells, and diffusely outlined In most instances they were surrounded by delicate connective tissue fibrils arranged somewhat concentrically In the center of the follicles the remains of obliterated blood vessels were apparent and, in the immediate vicinity of these, the lymphoid cells were densely packed At the periphery of the follicles the lymphoid cells were scanty in number and loosely arranged and were gradually lost in the interstices of the connective tissue strands by which the follicles were surrounded Between the follicles the substance of the organ was diffusely permeated by delicate connective tissue fibrils, frequently arranged in the form of slit-like apertures lined by endothelial cells In the lining endothelium mitotic figures were occasionally to be seen Most of the sinuses were empty, others were partly filled by endothelial and lymphoid cells and red blood corpuscles Lying in many of the sinuses and almost or completely filling them were multinucleated giant cells which were provided with an abundance of pinkish homogeneous or finely granular cytoplasm In some of the giant cells the nuclei were small and fairly uniform in outline and lay heaped up in the center of the cell body In others the nuclei varied in shape and size and in chromatic richness, and presented evidences of fragmentation in the form of deep indentations These giant cells were evidently derived from the endothelium of the sinuses the nuclei apparently attempting at first to divide by karyokinesis and later resorting to a process comparable to simple fragmentation Eosinophiles were unusually abundant There were no evidences of necrosis

This case represents in my opinion an example of primary Hodgkin's disease of the spleen and is remarkable from the standpoint of origin only I have not been able to find an exactly similar case in the

literature Donhauser[11] recently has reported a case of splenomegaly occurring in association with tuberculosis of the mesenteric lymph nodes and sclerosis of the bone marrow, in which the microscopical examination of the spleen bore a resemblance to that just described, in that there was considerable hyperplasia of the interstitial connective tis-
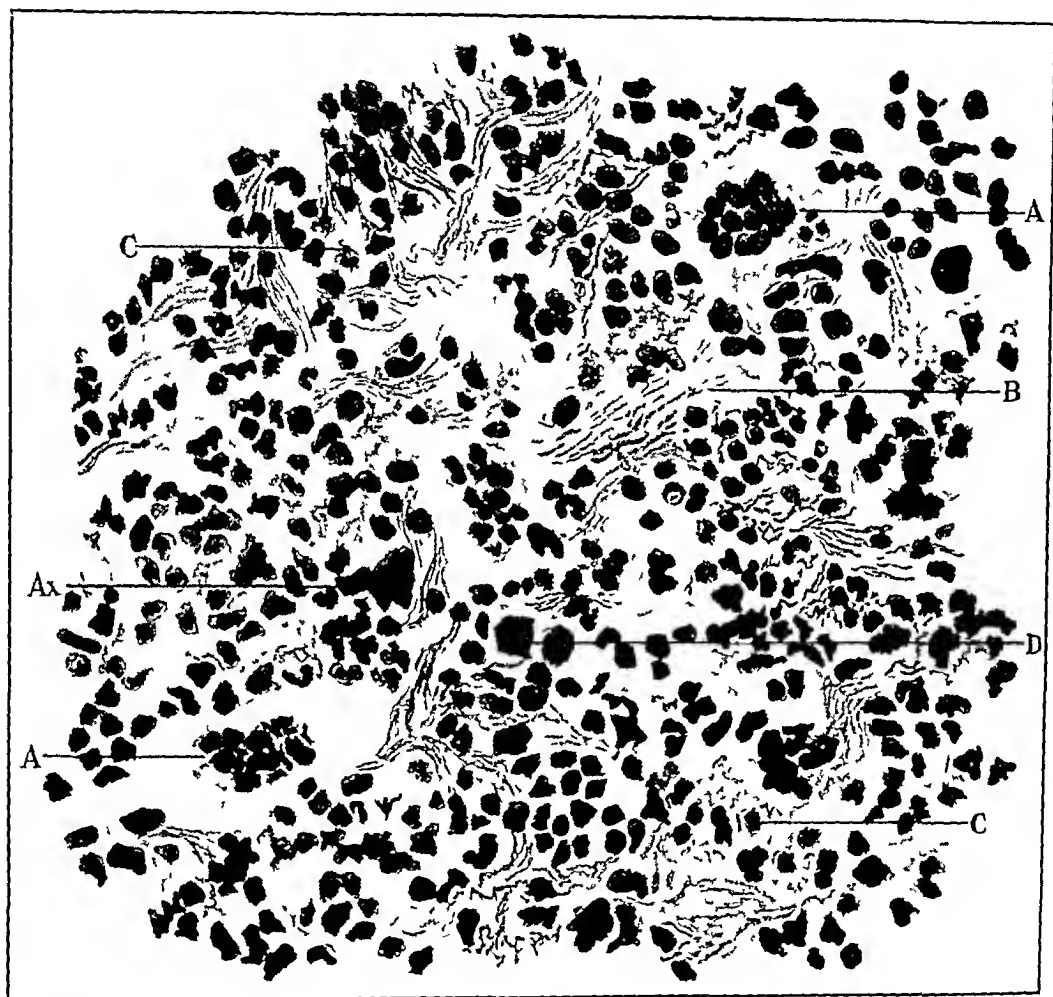
Fig 1 —Primary Hodgkin s disease of the spleen, specimen from Case 1   A, giant cells, Ax, shows the early formation of giant cells, probably of endothelial origin B areas of fibrosis, C, eosinophiles, D, endothelial cells   Drawn with Edinger's apparatus

sue, together with atrophy of the follicles and an occasional multi-nucleated giant cell In addition however the spleen presented to the naked eye numbers of large and small, circumscribed, spherical nodules

11 Donhauser   Bull Ayer Clin Lab Pennsylvania Hosp, 1908, v 46

which, on microscopical examination, were found to represent islands of hemopoietic tissue

CASE 2—Primary Hodgkin's disease of the retroperitoneal lymph nodes, secondary granulomatous lymphomata in the liver, kidney, spleen and bone marrow L G B, male, white, aged 31, admitted to the New York Hospital October 19, died Oct 30, 1904

History—The patient sought admission to the hospital because of progressive loss of flesh and strength He stated that his illness began fourteen months before, with symptoms which led his physician to treat him for malaria Two months before admission the patient's abdomen began to enlarge Seven weeks later about two gallons of fluid were withdrawn During the eleven days that the patient was under observation the evening temperature varied between 100 and 101 F

Physical examination revealed marked emaciation, with pallor of the visible mucous membranes The superficial veins over the abdomen were enlarged and the abdomen was distended by fluid

Blood Count—
    Red cells, 2,574,000
    White cells, 10,000
    Hemoglobin, 65 per cent
Differential Leucocyte Count—
    Polynuclear leucocytes, 84 per cent
    Small lymphocytes, 15 per cent
    Large lymphocytes, 1 per cent
The superficial lymph nodes were not palpable

On October 20 the abdomen was opened by median incision and 8 pints of clear yellow fluid escaped Enlarged glandular masses were observed at the hilum of the liver and in the gastrohepatic omentum Four days later the patient died after almost constant hiccoughs

Abbreviated Autopsy Protocol—Inspection The body was markedly emaciated On opening the peritoneum a small amount of fibrinous exudate was found near the lower end of the wound

Chest   Negative

Spleen   The spleen was somewhat flattened between the stomach and the left lateral abdominal wall and was increased to twice the normal size The organ was reddish in color and moderately firm in consistence Scattered over the surface were a few grayish bodies from 1 to 3 mm in diameter

Kidneys   Size increased   Capsules not adherent, cortices thickened cortical markings coarse and indistinct

Liver   Decreased in size reddish in color firm in consistence The surface presented several capsular cicatrices from 0 75 cm to 1 25 cm in diameter The general surface was irregular   On section the lobules were indistinct and a few grayish masses from 2 to 5 mm in diameter were found scattered through the substance of the organ

Stomach   Strong fibrous adhesions passed from the under surface of the liver to the hepatic flexure of the colon and to the stomach and first part of the duodenum   The stomach showed nothing unusual except that the pylorus was slightly thickened   There was no suggestion of a new growth   The pylorus looked upward and entered the concavity of a loop of intestine   This appearance was due to dilatation of the first part of the duodenum owing partly to fibrous adhesions to the liver and partly to the presence of an enlarged lymph node opposite the head of the pancreas

Lymph Nodes   The retroperitoneal lymph nodes in the upper part of the abdomen formed a large, grayish mass made up of numbers of nodes varying in size from 1 to 2 cm   These nodes were discrete and moderately firm in consistence   There was a single enlarged node in the lesser omentum that measured 3 by 1 5 cm   The mesenteric nodes presented no noteworthy naked eye changes

Microscopic Examination—Spleen   The normal structure of the spleen was largely replaced by the overgrowth of delicate connective tissue fibrils, scattered through the interstices of which were small numbers of lymphoid cells and numerous multinucleated giant cells, by large masses of hyaline connective tissue supporting still larger numbers of giant cells of the same type and by areas of
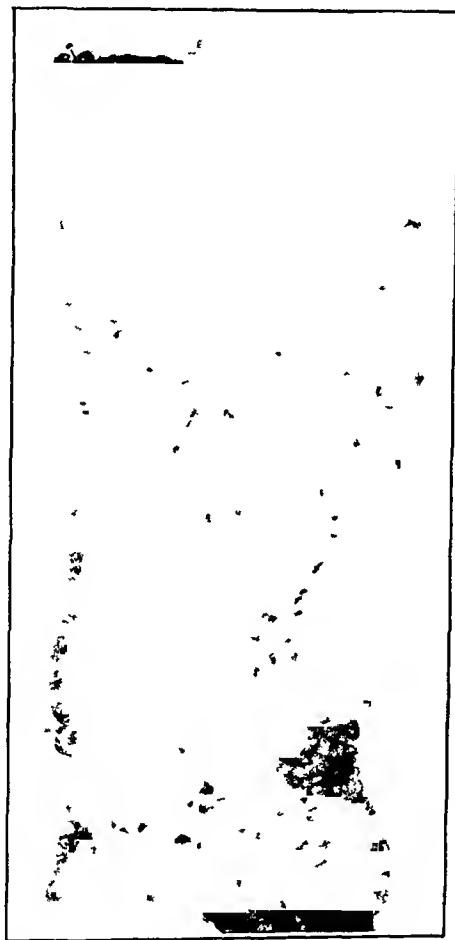
Fig 2 —Portion of large intestine from case of gastrointestinal pseudoleukemia (Case 4), showing widespread hyperplasia of the lymphoid follicles

anemic necrosis   Eosinophiles were entirely wanting   The lymphoid follicles were markedly atrophied

Lymph Nodes   Here, too, the normal structure was similarly replaced by the overgrowth of new tissue so that it was impossible to distinguish cortical follicles medullary cords or lymph sinuses   The framework of the node was made up of interlacing fibrils of connective tissue, among which were a few lymphoid and plasma cells and a large number of giant cells, some of which enclosed a single large nucleus, others multiple nuclei   Eosinophiles were not found   Areas of necrosis were visible here and there

Liver   In the liver the normal architecture was irregularly replaced by masses of tissue corresponding in all essentials to those already described in the spleen and lymph nodes   The main features in the evolution of the new tissue which was destined to replace the liver parenchyma could be readily traced   The earliest observable change consisted in the occurrence of small lymphomatous foci lying in the adventitia of the portal vessels   These foci gradually increased in size and cellular richness, invaded the perilobular connective tissue and finally encroached on adjacent liver cells, pushing them aside and infiltrating the intercolumnar capillaries   As the focus enlarged, minute connective tissue fibrils began to appear among the lymphoid cells and to form a supporting network for them, while large, oval or rounded cells with prominent vesicular nuclei and pinkish, finely granular cytoplasm could be observed here and there   In some instances, these latter cells were provided with delicate cytoplasmic processes   Eventually the liver lobules were invaded irregularly and replaced by masses of tissue made up of a delicately reticulated connective tissue network supporting large numbers of endothelioid and epithelioid cells and multinucleated giant cells   In other instances the liver lobules were destroyed and transformed into enormous necrotic foci, in some of which large hemorrhagic extravasations were visible

Kidney   Microscopical examination revealed marked granular degeneration of the epithelium of the convoluted tubules and the presence of hyaline casts   In the medulla, however, the picture was entirely different   Here the connective tissue supporting the blood vessels and straight tubules was richly infiltrated by lymphoid and plasma cells, the two varieties being present in about equal proportions   Among them were large numbers of typical multinucleated giant cells

Bone Marrow   The bone marrow revealed the presence of masses of tissue that showed essentially the same structure as those already described in the spleen, liver and lymph nodes, that is, there were numbers of lymphoid, epithelioid and giant cells, enclosed in a network of connective tissue

Aside from the fact that this case is an example of primary Hodgkin's disease of the retroperitoneal lymph nodes without cervical involvement, it is interesting from the standpoint of the histogenesis of the secondary visceral lesions, since the changes described in the liver indicate that the granulomatous masses are represented primarily by collections of lymphoid cells and that the other changes are sequential   In this connection another observation may be of interest   For example, a boy 16 years of age, presented himself at the New York Hospital in 1907, complaining of an enormous mass on the right side of the neck   A piece was excised for microscopical examination and was found to present the characteristic granulomatous lesions of Hodgkin's disease   A year later the boy returned to the hospital and a small lymph node was removed from the edge of the original growth   On microscopical examination this was found to present no changes on which the diagnosis of Hodgkin's disease could be based   On the contrary, the node presented the changes incident to diffuse lymphoid hyperplasia with proliferation of the cortical follicles   This tends to support the assumption that in the lymph nodes the initial manifestation of Hodgkin's disease consists in diffuse hyperplasia of the lymphoid cells, and that exhaustion

of these cells is accompanied or followed by connective tissue replacement and the other characteristic changes of the granulomatous lesion, to which reference has already been made

The histological observations just mentioned are in accord with Longcope's conclusion[10] that Hodgkin's disease is conceived in hyperplasia of lymphoid cells, that lymph nodes are being constantly regenerated in the course of the disease, and that these structures ultimately become the seat of granulomatous changes

CASE 3 —Primary Hodgkin's disease of the lymph nodes at the hilum of the liver   E W , Hebrew, single, aged 20, admitted to the New York Hospital April 25, 1908 , discharged June 1, 1908

History —On entering the hospital the patient stated that six weeks previously he began to experience sharp, lancinating pains in the right upper quadrant of the abdomen   These pains, although fairly constant, were worse at night and interfered with sleep   They continued for two weeks and then disappeared entirely, only to return four weeks later, when he sought admission to the hospital

Physical examination revealed a poorly nourished boy, whose visible mucous membranes were blanched   The conjunctivæ were faintly jaundiced   There was slight bulging in the lower part of the chest on the right side in front, and some tenderness and muscular rigidity in the right upper quadrant of the abdomen   A rounded mass was palpated 3 cm below the right costal margin and 1 cm below the edge of the liver, which was likewise felt   The mass appeared smooth to the touch and moved with respiration   No pain was experienced by the patient when the right costal margin was forcibly depressed   The spleen was not felt   The superficial lymph nodes were not enlarged   During the five weeks that the patient was under observation the evening temperature was practically always from 100 to 102 F

Blood Count—
        White cells, 7,800
        Hemoglobin, 80 per cent
Differential Leucocyte Count—
        Polynuclear leucocytes, 70 per cent
        Small lymphocytes, 22 per cent
        Large lymphocytes, 7 per cent
        Eosinophiles, 1 per cent
The urine was negative, except for the presence of urobilin

The patient was transferred to the surgical side and operated on by Dr Johnson   An incision 5 inches in length was made through the right rectus muscle   On opening the peritoneum a solid ovoidal mass about the size of a grapefruit was found projecting beneath the liver   It was not attached to the liver, gall bladder adrenal or kidney, but rested in a bed beneath the liver   The mass was removed

The surgical wound healed well and the patient eventually was referred to the Convalescent Home at White Plains

Anatomical Description —The specimen consisted of a large, heavy, ovoidal mass, 14 cm in length and about 10 cm in diameter   It was covered by a loosely

adherent connective tissue sheath, running through which were several large venous channels The mass was very firm in consistence, faintly yellowish or cream-colored, and the surface was smooth On section it cut firmly and the cut surface presented a yellowish translucent appearance and was faintly undulating Scattered over the cut surface, at remote intervals, were small hemorrhagic areas, together with aggregations of pin-point-sized, rounded, yellowish elevations, separated from one another by delicate depressions Running over the cut surface in different directions were coarse, pale, glistening, connective tissue bands

Microscopical Examination—Numerous sections were prepared from different parts of the mass It was found that the structure of the lymph node was not recognizable, but had been replaced by the growth of dense bands of hyaline connective tissue enclosing cellular islands of various shapes and sizes The picture was further confused by the presence of large necrotic foci and hemorrhagic extravasations In the connective tissue bands were a few scattered lymphoid cells, multinucleated giant cells and collections of eosinophiles The more cellular areas differed somewhat from one another in composition In practically every instance, however, cells of the fibroblastic type were so disposed as to form a more or less coarsely reticulated hyaline network supported in the meshes of which were variable numbers of lymphoid cells eosinophiles and multinucleated giant cells, together with enormous numbers of large flattened cells with large richly chromatic nuclei These were evidently endothelial cells and the progenitors of the multinucleated giant cells In several instances dense hyaline connective tissue bands were seen, which enclosed very small islands of tissue that bore a resemblance to tubercles, in that they were composed of somewhat concentrically arranged connective tissue fibrillæ with cytoplasmic processes which intercommunicated or were fused together thus forming a network in which were numbers of lymphoid cells Lying at the center, in most of these tubercle-like structures was a single giant cell with hyaline cell body and multiple nuclear fragments heaped up in the center and provided at its periphery with delicate filamentous processes These giant cells were surrounded by a clear space bridged over at intervals by the filamentous processes just referred to No tubercle bacilli were found in these localities nor, in fact in any other

Immediately on receipt of the specimen from the operating room frozen sections were made and the diagnosis of Hodgkin s disease was established An emulsion from the original mass was then made in sterile bouillon, and of this 2 c c were injected into the peritoneal cavity of a guinea-pig The results were negative

In this case we are provided with still another example of primary abdominal Hodgkin's disease, manifested clinically by a large tumor-like mass, originating, probably, in the lymph nodes at the hilum of the liver In addition to its interesting anatomical and histological features the case is instructive from the standpoint of the surgeon

PSEUDOLEUKEMIA

Shortly after Virchow described leukemia, Cohnheim[3] recorded a case which presented similar anatomical characteristics without changes in the blood For this disease he suggested the name of 'pseudo-leukemia' The patient was a man, aged 24, who suffered from anorexia,

vomiting and repeated attacks of epistasis   The leucocytes were considerably diminished in number and no abnormal forms were present At autopsy the spleen was greatly increased in size, measuring 10 by 7 by 3 5 inches, and presented innumerable hyperplastic lymphoid follicles   The liver was increased in size and, on microscopical examination, disclosed the presence of lymphomatous foci in the neighborhood of the portal vessels   The kidneys were enormously enlarged and, on microscopical examination, the interstitial tissues were found to be richly infiltrated by lymphoid cells   The cervical, inguinal and retroperitoneal lymph nodes were hyperplastic   The gastrointestinal tract presented no noteworthy changes

Nearly thirty years before the appearance of Cohnheim's paper, however, Briquet[12] had pictured a peculiar disease characterized by extensive hyperplasia of the lymphoid tissues in the gastrointestinal tract, and since then a few similar cases have been added to the literature These also are undoubtedly examples of pseudoleukemia and will be touched in more detail later

A case of this description recently came under observation at the New York Hospital and its clinical and anatomical features are presented below in some detail

CASE 4—Gastrointestinal pseudoleukemia   J M S, white, aged 42, single, porter   Admitted to the New York Hospital June 24, 1908, discharged June 26, 1908   Readmitted Dec 31, 1908, died Jan 1, 1909

History—One year before the date of the patients first admission to the hospital he noticed a painless swelling on the left side of the neck   It gradually increased in size and was followed six months later by the appearance of a similar mass on the opposite side   Three months later the patient began to have three or four stools daily   The stools were watery and defecation was painless   In the course of the next three months the stools increased to fifteen or twenty daily, and at the end of this time the patient sought admission to the hospital because of loss of strength and flesh

Physical examination revealed a poorly nourished adult male   The visible mucous membranes were pale, the teeth in poor condition, the gums infiltrated by pus   Both tonsils were enlarged, especially the left   In the left anterior triangle of the neck were two glandular enlargements, each the size of a large walnut In the left posterior triangle was an enlarged gland the size of a hazel nut   A mass of about the same size was present beneath the angle of the lower jaw on the right side   A number of smaller nodules was present on both sides of the neck, lying between the larger ones just described   The subclavicular nodes on both sides were palpable   The axillary nodes were enlarged to the size of marbles   All of the nodes were painless, discrete and freely movable

Blood Count—
     Red cells, 5,240,000
     White cells, 11,000
     Hemoglobin, 80 per cent
     Color index, 0 8

12 Briquet   Cruveilhier s Atlas, 1835-42, ii, 34

Differential Leucocyte Count—
>   Polynuclear leucocytes, 72 per cent
>   Small lymphocytes, 24 per cent
>   Large lymphocytes, 3 per cent
>   Eosinophiles, 1 per cent

The patient s temperature on admission at 3 p m was 99 F, normal thereafter Examination of the stools revealed the presence of blood The urine was negative At the end of forty eight hours the patient was discharged at his own request

About midnight of Dec 31, 1908, the patient was admitted to the hospital *in extremis*, presenting the classical signs of acute peritonitis He died a few hours later so that it was not possible to obtain any information concerning his condition during the six months which had elapsed since he came first under observation A blood examination at this time revealed a leucocytosis of 14,400 and a preponderance of polynuclear leucocytes It is also interesting to note that just before death digital examination of the rectum was made by one of the house surgeons and numerous small nodules were felt scattered through the mucous membrane

Abbreviated Autopsy Protocol—The autopsy was performed four and a half hours postmortem

Inspection The body was that of a man 42 years of age, 170 cm in height, of large, well-developed frame, poor musculature and nutrition The skin and visible mucous membranes were very pale In the region of the left parotid gland and extending downward into the neck was a globular swelling, half again as large as a hen's egg This lay immediately beneath the skin, was elastic to the touch and freely movable There was a similar but somewhat smaller mass just below the angle of the jaw on the right side Beneath the skin covering the front of the chest were a few masses of like description, the largest of which was flattened and about the size and shape of the thumb nail The skin over the anterior chest and over the lower aspect of both legs presented a number of pin-head-sized, hemorrhagic petechiæ

Peritoneum The abdomen contained a large quantity of cloudy fluid in which were numbers of gelatinous clots The peritoneum was opaque and irregularly covered by fibrinous exudate The intestinal loops were frequently matted together by fibrinous material, beneath which the serosa was opaque and irregularly injected

Lungs Emphysematous, otherwise entirely negative

Spleen The spleen measured 15 by 10 by 5 cm The shape was well preserved Seen through the capsule it presented a grayish-red color The capsule was thin and tense On section the organ cut firmly The cut surface was pinkish in color Scattered over the cut surface were innumerable large and small, rounded or irregularly outlined, pale, translucent bodies These were arranged in close proximity to one another and the scanty amount of tissue between them was opaque and pinkish, thus the cut surface presented a coarsely speckled appearance Some of the larger translucent bodies were intersected by delicate reddish lines The consistence of the organ was noticeably increased, imparting a fine grating sensation when crushed between the fingers Lying at the hilum were a half dozen lymph nodes, the largest of which measured 4 cm in length and 1 cm in thickness The nodes were pale discrete and elastic to the touch On section, the cut surface was pale and sprinkled over with minute reddish points, thus giving the whole a finely mottled appearance

Adrenals and Semilunar Ganglia Negative

Kidneys   These organs were considerably increased in size and presented the characteristic naked eye appearance of an acute diffuse hemorrhagic nephritis

Liver, Gall Bladder, Pancreas, Urinary Bladder, Abdominal and Thoracic Aortas, Prostate, Testicles and Ureters   Presented no noteworthy naked eye changes

Bone Marrow   The marrow of the vertebræ was diffusely bluish-red in color

Lymphoid Apparatus   The tongue, larynx, esophagus, thyroid gland, stomach, pancreas and liver were removed *en masse*, together with numbers of enlarged lymph nodes from the lateral region of the jaw on both sides and from the neck, thorax and abdomen   The tongue presented moderate numbers of hyperplastic lymphoid follicles at the base   Large numbers of tumor-like masses were removed from the region of the left parotid gland, from beneath the angle of the lower jaw on the right side, from the sides of the neck, esophagus and trachea as low down as the bifurcation of the latter   The peribronchial lymph nodes were markedly enlarged and faintly anthracotic   In these several situations the size of the individual nodes varied from that of a pea to a hen's egg   Many of the smaller nodes were entirely discrete   In other instances large numbers of nodes of varying dimensions were clustered to form masses the size of a child's fist This was specially true of the upper cervical region   Each node was enclosed in a definite connective tissue capsule which served to separate one from the other On section, the nodules were moderately firm in consistence and presented a smooth, pale or faintly pinkish, homogeneous, glistening surface, intersected at the periphery, in occasional instances by coarse yellowish lines derived from the cap sule   In many of the nodules minute reddish points could be seen here and there or faint reddish lines were visible running across the cut surface   The mesentery was enormously thickened through the presence in it of dozens of pale, rounded masses   each enclosed in a connective tissue capsule which separated them from each other and from the peritoneal covering of the mesentery   These nodes varied in size from a small marble to a crab apple and, on section, presented essentially the same naked eye appearance as those elsewhere described   At the hilum of the spleen were small numbers of enlarged, discrete lymph nodes   The pancreas was literally embedded in enlarged nodes, many of which were entirely discrete

Stomach   The walls of the stomach were greatly thickened   The rugæ were unusually numerous and very prominent   Between them the mucous membrane presented vast numbers of pale, opaque, nodular masses, separated from one another by shallow crypts   In the pylorie region these nodules were still more numerous and prominent, where they appeared as discrete, rounded or conical, closely apposed elevations about 0 5 cm in height   On section, they appeared to be limited to the mucosa and presented a pale, homogeneous surface

Intestine   The walls of the intestine throughout were greatly thickened   The lumen of the intestine was large, the mucous membrane pale or cream colored Scattered through it, from the pyloric end of the stomach to the anus, were myriads of nodular masses of different sizes   These were arranged in such close proximity to one another that the intervening mucous membrane was scarcely visible   In the mucous membrane of the duodenum immense numbers of small, rounded nodules were separated from one another by small sheets of tissue made up of pin head-sized follicles   In the jejunum the rugæ were exceedingly large Distributed through the mucous membrane, lying partly along the summit of the rugæ and thickly dispersed through the mucosa between the rugæ, were hundreds of pale, nodular projections, varying from the size of the head of a pin to that of

a large pea   For the greater part these bodies were conical in shape and rested upon a broad base embedded in the mucous surface of the intestine, a few were attached by delicate pedicles and hung free in the lumen   Here and there these nodules were aggregated to form cauliflower-like excrescences from 2 to 4 mm in height   Essentially the same general description applies to the mucous membrane of the ileum throughout its entire extent, except that the cauliflower-like excrescences were even more numerous, and hyperplastic Peyer's patches came into view   These latter bodies were present to the number of a dozen or more and were roughly quadrangular in outline and from 2 to 7 cm in length and 2 to 4 mm in height   The mucous membrane of the cecum presented a cream-colored, velvety appearance and was thrown into massive folds that were arranged more or less concentrically   At the commencement of the ascending colon was a pedunculated mass, 4 cm in height, the surface of which was traversed by a few shallow furrows   The mucous membrane covering the mass was smooth and slate-colored   On section the cut surface of the mass was pinkish in color and smooth   In the mucous membrane of the large intestine, from the ileocecal valve to the anus, were literally thousands of closely aggregated, pale, rounded, nodular projections, varying in size from a millet-seed to a split pea   Many of them presented small crater-like depressions at the summit   In this part of the intestine the transverse folds of the mucous membrane were enormous and were capped by numbers of rounded nodules, many of which were deeply pigmented   The nodules lying in the mucous membrane between the folds were pale and thickly set together, so that the contrast between the rugæ and the intervening surface was very striking

Anatomical Diagnosis —Chronic sclerotic localized pericarditis, brown atrophy of heart, emphysema, lymphoid hyperplasia of spleen, chronic interstitial splenitis, acute diffuse exudative hemorrhagic nephritis, multiple angiomata of liver, stasis, acute diffuse purulent peritonitis, lymphoid hyperplasia at the base of the tongue, lymphomatosis of the cervical, thoracic and abdominal lymph nodes and of the gastrointestinal tract (pseudoleukemia)

Microscopical Examination —Spleen   The lymphoid follicles were unusually numerous and varied in size within considerable limits   Most of them, however, were distinctly increased in size, rich in cells and definitely encircled by bands of delicately fibrillar connective tissue, enclosing within its meshes moderate numbers of lymphoid cells   In other instances the follicles were irregularly intersected by trabeculæ of fibrillar connective tissue that served to divide them into cellular islands of variable shapes and sizes   In still other places the follicles were very small and were surrounded by masses of loosely arranged connective tissue, that appeared to be closing in equally on all sides, thus tending to replace the follicle as a whole   That such a replacement was eventually effected at times was evidenced by the fact that here and there were rounded islands of tissue made up of a rather coarsely reticulated network, supporting focal collections of lymphoid cells   In still other instances the follicles were invaded and partially replaced by masses of connective tissue, supporting considerable numbers of slit-like apertures that were filled by red blood corpuscles   The vessels of the follicles practically everywhere were thickened and hyaline in appearance and their lumina were partially or completely obliterated   Between the various follicles the splenic pulp was extensively replaced by a delicate interlacement of connective tissue fibrillæ   The interstices between the individual fibrils contained considerable numbers of lymphoid cells, others were filled by red cells   The connective tissues also supported numerous small sinuses lined by endothelial cells   Most of these sinuses were occupied by lymphoid cells, others by red blood corpuscles

TABULAR PRESENTATION OF CASES OF GASTROINTESTINAL PSEUDOLEUKEMIA

Case No	Sex	Age	Superficial Lymph Nodes	Abdominal Lymph Nodes	Gastro-intestinal Tract	Spleen	Liver	Blood	Author Reference	Remarks
1	M	11	Hyperplasia of faucial and inguinal tonsils and of inguinal lymph nodes	Greatly enlarged	Rugæ of stomach enormously thickened Hyperplastic follicles and polypoid masses throughout small intestine Peyer's patches in lower ileum enlarged Polypoid and sessile follicles in large intestine Appendix greatly thickened				Briquet[1]	
2	F	73	Cervical and inguinal nodes enlarged	Mesenteric glands greatly enlarged	Stomach studded over by large and small cream colored, flattened tumors Similar masses present in small intestine below duodenum Solitary follicles and Peyer's patches greatly enlarged Enormous fold like thickening of mucous membrane of ileocecal valve	Weight 1,320 gms Follicles markedly hyperplastic		Red cells, 4,720,000, 13 white cells to 1000 red cells	Carrington[16]	General wasting for 6 mos No abdominal symptoms
3	M	51	Cervical, axillary and inguinal glands enlarged		Solitary lymphomatous nodules near pyloric end of stomach Enlargement of solitary and agminated follicles from duodenum to anus	Size 25×37.5 cm, studded with white nodules	Solitary lymphomatous nodule		Haddon[17]	Emaciation
4	M	18	Marked hyperplasia of faucial and inguinal tonsils	Mesenteric nodes enlarged	Large polypoid, sessile and vermiform thickenings in stomach together with smaller raised, flattened nodules Innumerable lymphomatous nodules in small gut Peyer's patches enlarged Colon free	Weight 765 gm Follicles markedly hyperplastic			Pitt[18]	
5	M	62	General enlargement of superficial lymph nodes	Enlarged	Polypoid masses and sinuous folds in stomach Flattened elevated patches in small intestine through out Elevated patches and polypoid outgrowths in colon Appendix greatly thickened	Three times normal size Follicles greatly enlarged		Red cells, 2,100,000, Hb, 55 % No leuco cytosis	Schlesinger[19]	

No.	Sex	Age	Lymph nodes	Other nodes	Gross findings	Follicles	Smaller foci	Blood	Reporter	Symptoms
6	M	50	Great enlargement of cervical glands. Nares filled by lymphomatous masses. Tonsils hyperplastic	Greatly enlarged	Stomach diffusely invaded by lymphomatous nodules. Enlarged follicles in esophagus. Solitary and agminated follicles throughout small intestine hyperplastic. Cecum filled by pigmented nodules. Appendix thickened and nodular. Follicles in colon enlarged	Solitary lymphomatous nodule			Herrick[20]	Lymphomatous masses in the lungs
7	F	57	Hyperplasia of faucial and lingual tonsils and of cervical and inguinal nodes		Mucosa of stomach greatly thickened and thrown into folds. Pea-sized nodules between folds. Hyperplasia of solitary and agminated follicles of small gut and of follicles of colon	Size 16×10×4 cm. Follicles enlarged			Stoerck[21]	Diarrhea alternating with constipation, blood in stools. Great abdominal pain
8	M	51	Universally but slightly enlarged	Enlarged	Mucous membrane of stomach diffusely thickened, in places nodular. Solitary follicles and Peyer's patches hyperplastic. Appendix thickened	Enlarged Follicles hyperplastic	Numerous small foci, lymphomatous		Wells[3] and Mayer	Lymphomatous foci in esophagus, kidneys, pancreas, prostate and adrenals. Anemia, night sweats, "poor digestion," prostration, tenderness in epigastrium
9	M	48	Right cervical nodes enlarged. Large mass in left inguinal region	Perigastric and peripancreatic nodes enlarged	Polypoid and nodular masses in stomach. Hyperplastic follicles in upper half of duodenum and throughout jejunum and ileum. Peyer's patches enlarged. Follicles in colon enlarged throughout. Fungoid mass in cecum	Slightly enlarged Follicles hyperplastic	Numerous lymphomatous foci	Leucocytes, 10,600	Celler[15]	Intussusception at ileocecal valve
10	M	12	Faucial and lingual tonsils enlarged. Cervical nodes on both sides	Enlarged	Enlargement of rugae in stomach with nodular masses. Nodular lymphomata from pylorus to anus. Polypoid masses in jejunum. Peyer's patches enormous. Large sinuous folds in cecum	Markedly enlarged Follicles very prominent	Microscopic lymphomata	Red cells, 5,240,000; leucocytes, 11,000. Hb, 80%	Symmers	Purulent infiltration of gums, 15 to 20 bloody stools daily
11	F	11	Enlarged inguinal and cervical nodes	Enlarged	Thirty cm of small intestine excised at operation and found studded with nodules. (Balance of gastrointestinal tract not examined, but probably involved.) Peyer's patches enlarged. Several polypoid tumors in excised intestine	Not enlarged			Hoffman[4]	Diarrhea persistent. Occasional vomiting. Intussusception at ileocecal valve

Liver   The only noteworthy microscopical change in the liver consisted in the occurrence of numbers of small, richly cellular lymphomatous foci, lying in the connective tissues of the periportal spaces and probably derived from the outer sheath of the portal veins

Kidneys   The microscopical changes corresponded to those usually found in acute diffuse hemorrhagic nephritis

Lymph Nodes   Numbers of microscopical preparations of nodes removed from various parts of the body were examined   All of them showed essentially the same changes The normal architecture of the node was markedly altered, so that the distinction between cortex and medulla was entirely lost   Neither lymph follicles nor sinuses were distinguishable   The node was surrounded by a moderately thick connective tissue capsule through which small numbers of lymphoid cells were dispersed   Connective tissue trabeculæ, derived from the capsule, penetrated the node at different intervals and divided the substance of the organ into large, densely cellular islands of lymphoid tissue   Among the lymphoid cells were moderate numbers of large rounded cells with abundant pinkish cytoplasm These cells were provided with a single large rounded or indented nucleus or, in some instances, with two or three nuclei   The connective tissue trabeculæ were broad and made up of exceedingly delicate, loosely woven fibrils sprinkled through the meshes of which were relatively small numbers of lymphoid cells The connective tissue bands were dispersed through the substance of the node in a more or less regular fashion, and their pale, non cellular appearance formed a striking contrast to the large, densely cellular lymphoid islands around which they were disposed   Microscopical examination of the discrete nodes described in the protocol as reddish in color or faintly speckled revealed a slightly modified picture   In these nodes large, densely packed masses of lymphoid cells were separated from one another by thin bands of coarsely reticulated connective tissue supporting numerous deeply injected vascular channels with thick, hyaline walls

Intestine   Sections removed for microscopical examinations from the nodular areas in different parts of the intestine disclosed the presence of enormous lymphoid collections occupying the mucosa and submucosa, replacing and almost completely destroying the glandular elements   Arranged around the periphery of the individual nodules were numbers of small, circumscribed, richly cellular lymphoid foci that stood out in strong contrast to the interior or medullary substance, which was composed of loosely arranged, diffusely distributed lymphoid cells

This case is interesting from several standpoints   In the first place, it presents certain clinical features that are suggestive of Hodgkin's disease, in that the initial visible manifestations of the process occurred in the cervical region in the form of slowly progressive glandular enlargements that were discrete, painless and freely movable beneath the skin These were accompanied by advancing asthenia and cachexia and by the blood picture that is usually found in Hodgkin's disease, in fact, in the absence of a microscopical examination of the glandular masses during life, the case was actually regarded as one of Hodgkin's disease. Death occurred after the lapse of eighteen months and the anatomical distribution and naked-eye appearances of the enlarged glands fulfilled the requirements of Hodgkin's disease as seen at autopsy   The widespread lymphoid hyperplasia in the gastrointestinal tract, however, stood

out in marked contrast to all the known lesions of Hodgkin's disease
The absence of changes in the blood and of leukemic infiltration of the
viscera served, among other things, to distinguish the disease at once
from true leukemia   It remained, however, to classify the case with
regard to its relation to pseudoleukemia as conceived by Cohnheim, and
to the changes described by Steinberg as a peculiar form of lymphatic
tuberculosis and later described in this country by Reed as a non-tuber-
culous lesion forming the sole histological basis of the clinical entity
known as Hodgkin's disease   In this connection I think it has been
made clear from the description of the histological changes that the
case belongs in the former category and that it probably bears no rela-
tionship to Hodgkin's disease

This case, too, while noteworthy, is not unique   Thus, in an exten-
sive review of the literature, Wells and Mayer[13] were able to collect
reports of seven cases of gastrointestinal pseudoleukemia in which the
changes in the lymphoid tissues were no less remarkable than those just
described   These observers added another case, and recently Hoffmann[14]
and Celler[15] have each reported a case, so that the one described in
the present paper brings the total number to eleven   I have attempted
to collate the chief points of interest in all these cases and to present
them in the accompanying table

ANALYSIS OF TABLE

While the number of cases of gastrointestinal pseudoleukemia avail-
able for analysis is not sufficient to warrant general deductions, several
interesting points of similarity are apparent

Eight of the eleven cases occurred in males, the youngest subject
being 41 years of age, the oldest 62

In spite of the extensive anatomical alterations in the stomach and
intestines, definite clinical symptoms referable to these changes are
recorded in five instances only   Thus, in Stoerck's case, there was a
history of diarrhea alternating with constipation, of bloody stools and
abdominal pain   In Hoffman's case the patient complained of persistent
diarrhea and vomited occasionally   In my own case there was a history
of prolonged and severe diarrhea attended by blood in the stools   In
Wells and Mayer's case there is an indefinite reference to digestive dis-
turbances   In two cases intussusception occurred

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13 Wells and Mayer   Am Jour Med Sc , 1904, cxxviii, 837
14 Hoffman   Arch f klm Chir 1907 lxxxii, 794
15 Celler   Tr New York Path Soc , 1908, viii, 148

The anatomical picture, however, is more uniform   In practically
every case the superficial lymphoid structures were more or less en-
larged   Thus the faucial and lingual tonsils were enlarged in five cases,
while hyperplasia of the superficial lymph nodes was almost constant,
especially in the cervical region, being absent in one case only   The
spleen was enlarged in eight instances, depending, apparently, on hyper-
plasia of the lymphoid follicles   In 4 cases small lymphomatous foci
were present in the interlobular connective tissue of the liver

In the gastrointestinal tract the changes varied both in extent and
location   Great thickening of the walls of the stomach was practically
constant and in most instances the mucous membrane was thrown into
massive vermiform folds   Between the folds the lymphoid tissues were
markedly hyperplastic, appearing as nodular masses or as polypoid pro-
jections   In the intestine the duodenum presented more or less marked
evidence of lymphoid hyperplasia in seven cases   Similar but more ex-
tensive changes were constant in the jejunum, where polypoid masses
frequently were encountered   Widespread hyperplasia of Peyer's patches
was a constant feature   In four instances the appendix was markedly
thickened   In two cases the mucous membrane of the cecum was thrown
into large sinuous folds   Lymphoid hyperplasia of the follicles in the
large intestine was present in nine cases, most often in the form of dis-
crete nodules, but sometimes in the form of polypoid outgrowths   In
nine instances the abdominal lymph nodes were enlarged, sometimes to
an enormous extent

SUMMARY AND CONCLUSIONS

1   Whether Sternberg be correct in his contention that the changes
in Hodgkin's disease are tuberculous is a problem with which this paper
is not directly concerned, but, in view of the doubtful etiology of the
disease and the several synonyms which have been incorrectly applied,
it seems desirable, in the light of the specific histology which has been
established for the process, to coin some term which will describe its
microscopical peculiarities and serve, at the same time, to distinguish
the disease from pseudoleukemia and other lesions with which it has
been confounded   For these purposes the term "Hodgkin's granulo-
matous lymphoma" appears to be suitable, since it designates the type
of tissue in which the disease commences, the initial changes by which
it is characterized, and the secondary changes that occur in the course
of its development, while it reserves to Hodgkin the recognition that is
due him   At all events, it is scarcely justifiable to employ the term
'pseudoleukemia' as a synonym for "Hodgkin's disease" since the two

processes, when fully developed, are readily separable and present totally different histological alterations

2 From the histological features described in the spleen in the case first presented I think it is shown that there is a primary splenic form of Hodgkin's disease, while Cases 2 and 3 serve to emphasize the fact that the abdominal lymph nodes may be the seat of origin

3 The histogenesis of Hodgkin's disease, both in the lymphatic system proper and in the viscera, appears to be conceived in the formation of lymphomatous foci, while the characteristic granulomatous changes are sequential

In conclusion I wish to acknowledge my gratitude to Dr Harrison S Martland, pathologist to the Newark City Hospital, for the drawing in the case of primary splenic Hodgkin's disease and to Dr Charles E Farr for the photograph of the intestine in the case of pseudoleukemia.

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19. Schlesinger   Ztschr f klin Med, 1897, xxxii, Suppl Heft, 179
20 Herrick   Tr Chic Path Soc, 1897-99, iii, 345
21 Stoerck   Wien klin Wchnschr, 1904, xvii, 4

SPHYGMOGRAPHIC STUDY OF A CASE OF COMPLETE HEART-BLOCK

A CONTRIBUTION TO THE STUDY OF THE ACTION OF STROPHANTHUS ON THE HUMAN HEART [*]

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One of the most interesting of the disturbances of cardiac function is the one known as heart-block, a condition in which the auricular and ventricular rhythms are dissociated and in which a most notable infrequency of the pulse is usually observed   The experimental work of Humblet,[1] Hering,[2] and of Erlanger[3] on the atrioventricular bundle of His and the concomitant observation that heart-block may occur spontaneously in man have so stimulated the study of bradycardia that, within a few years, a relatively large number of cases presenting the phenomenon of auriculoventricular dissociation has been reported   Dissociation of the contractions of auricles and ventricles is most often found in patients suffering from the Adams-Stokes syndrome   There have been, however, a few undoubted cases exhibiting the symptom-complex of permanent bradycardia in association with syncopal or epileptiform attacks, in which the condition of auriculoventricular dissociation could be definitely excluded (Lépine[4])   On the other hand, heart-block, either complete or incomplete, has been found in cases in which there were at no time any of the nervous phenomena which characterize the

Adams-Stokes syndrome (Mackenzie,[5] Joachim,[6] Gerhardt,[7] James,[8] Chauffard,[9] Gibson,[10] Jellinek and Cooper,[11] Bachmann[12]) Heart-block, of a transitory character, may also be observed in digitalis poisoning

The observations recorded in the present paper were made on the patient presenting the Adams-Stokes symptom-complex whose clinical history will be reported by Dr Kalteyer later

The notably infrequent pulse and the presence of relatively frequent faint fluttering pulsations at the root of the neck made one suspect the cause of the bradycardia to be dissociation in the action of auricles and ventricles The movements of the apex beat, carotid and jugular pulses were accordingly recorded in order to decide this question
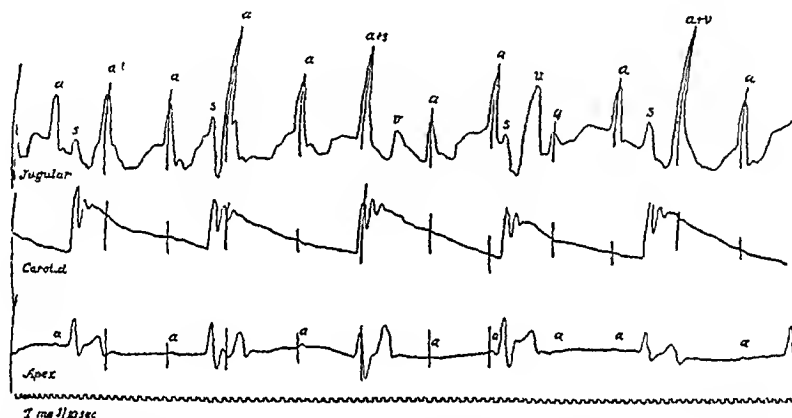
Fig 1 —Simultaneous tracings of pulsations in the right internal jugular vein, carotid artery and of the apex-beat (Dec 30, 1908)

Figure 1 is one of the tracings obtained during the first days of the patient's stay in the hospital This tracing shows that the ventricular contractions were infrequent and regular, and that each of these was

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followed by a carotid pulsation, the auricular contractions (a), as reflected in the jugular pulsations, were from two to three times as frequent as the ventricular contractions The auricles and ventricles exhibited, therefore, a different rhythm, each rhythm, moreover, bearing no definite relations to the other In other words, the ventricular contractions were absolutely independent of the auricular contractions, and the notable bradycardia observed in the patient was due to the failure on the part of the auricles to excite the ventricles to contraction There was, therefore, a complete block to the passage of the excitation wave from the auricles to the ventricles, and the latter were beating by virtue of their own power of rhythmic stimulus-production

The ventricular and auricular rates of contraction during the first days the patient was under observation are given in Table 1
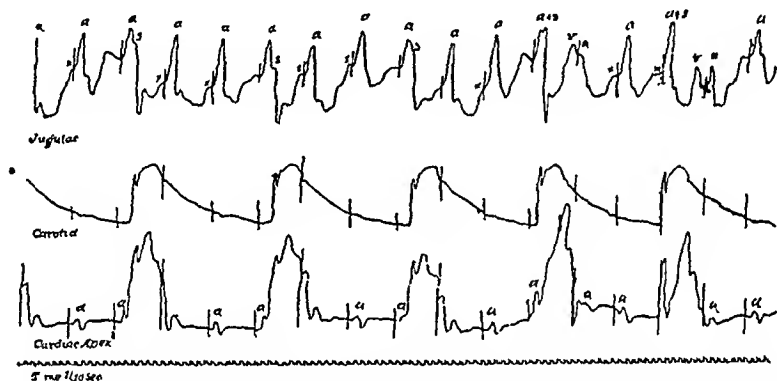
Fig 2 —Tracing showing a well marked "sinus wave" This wave, attributed to the contraction of the mouth of the precava, is marked by an X (Dec 31, 1908)

TABLE 1

Date	No of Vs	Duration in 1/10 sec	No of Vs per min	No of As	Duration in 1/10 sec	No of As per min	As Vs
Oct 27, 1908	13	206	37 86	34	238	85 71	2 26 1
Oct 28, 1908	23	411	33 57	53	424	75	2 23 1
Oct 30, 1908	19	352	32 38	44	359	73 53	2 27 1
Oct 30, 1908	18	345	31 3	43	364	70 87	2 26 1
Oct 30, 1908	15	283	31 8	38	313	72 84	2 29 1
Average	—	—	33 38	—	—	75 59	2 26 1

A closer analysis of the tracing (Fig 1), which may be used as a type, shows in the record of the jugular pulsations a number of positive waves of unequal heights Those marked *a* are referable to the contractions of the right auricle those marked *s* are due to the upward projection of the tricuspid valve into the cavity of the auricle at the beginning of ventricular systole These correspond to the wave usually designated *c,* and in this instance it is often vitiated by the pulsation

of the subclavian artery, owing to the latter's abnormally high position above the clavicle The third positive wave, *v,* is probably attributable to the relaxation of the papillary muscles and the ascent of the auriculo-ventricular septum at the end of ventricular systole The height of the auricular waves varies according to the time of occurrence of the auricular contractions, being very high when the auricular contraction

Fig 3 —Tracing from the right radial artery There are no abnormal waves on the katacrotic limb of the pulse wave as seen in most of the other tracings obtained from the carotid artery

takes place during ventricular systole, and very low when the auricular contraction occurs shortly after the beginning of ventricular diastole This finds its explanation in the ventricular pressure changes occurring during the cardiac cycle If, when the ventricle is in a state of contraction, the auricle suddenly contracts, the rise of intra-auricular pressure which follows is sufficient to overcome the high intraventricular
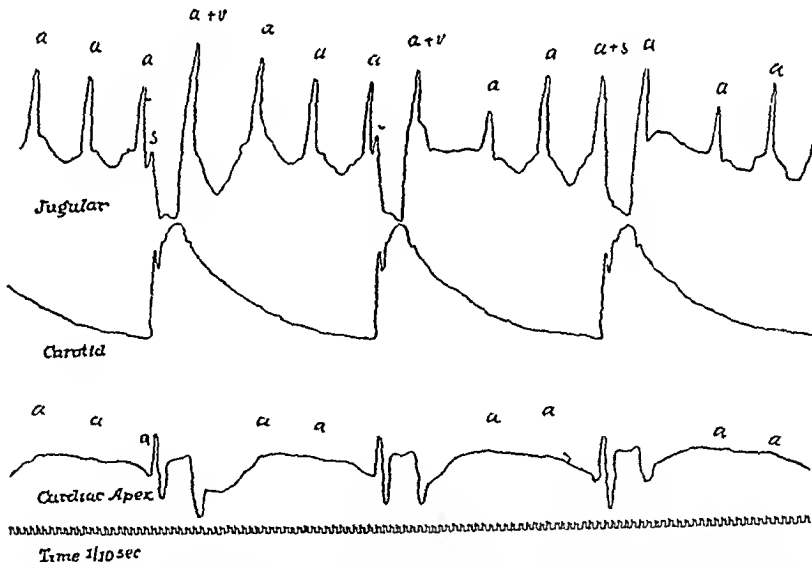
Fig 4 —Tracing taken on Nov 19, 1908, at a time when the syncopal and epileptiform attacks had become more frequent and more severe The apparent 4 1 rhythm is purely accidental

pressure, and the auricular blood will be forced backward into the large veins, which in consequence will be suddenly and forcibly distended When the auricular contraction takes place, either at the beginning or toward the end of ventricular systole, the resulting wave is also very high This high wave is due, in the first instance, to the addition of the *s* to the *a* wave, in the second instance, to a blending of the *v* with

the *a* wave In either case the resulting compound wave is generally higher than either wave taken separately A small wave immediately preceding the *a* wave can be seen in most of the tracings illustrating this article This wave has been observed and described by Erlanger and by Gibson, and has been attributed by them to the contraction of the mouth of the vena cava (sinus contraction), it is more likely to appear when the veins are well filled This *sinus* wave is especially well de-
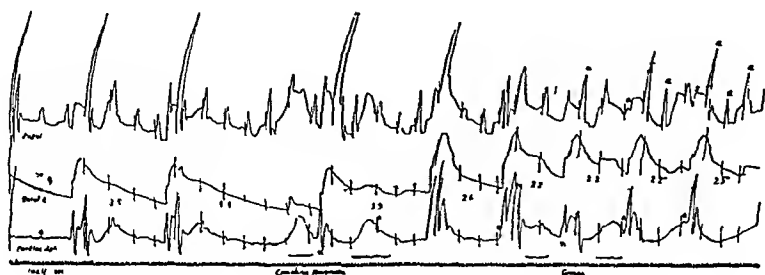
Fig 5 —Tracing taken during a short attack

fined in Figure 2, which was taken on a day (Dec 31, 1908) when the jugular veins were more distended than usual

The carotid pulse in nearly all the tracings is of the anacrotic type and has the rounded summit typical of the senile pulse There are faint indications of small waves on the katacrotic limb of the pulse wave outside of those normally found there They bear a definite relation to the *a* waves of the jugular pulse, and are in all probability due to the
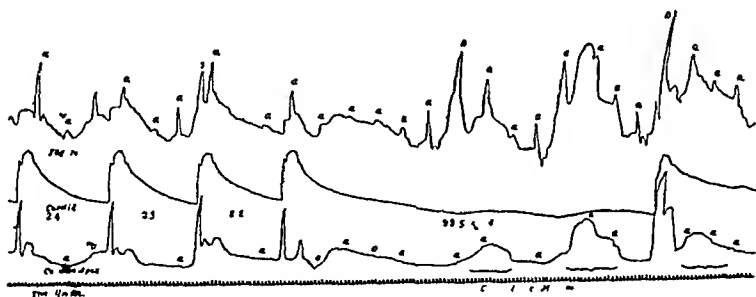
Fig 6 —Tracing taken during a longer attack Note the prolonged stoppage in the ventricular contractions and that the convulsive movements do not occur until toward the end of the ventricular silence The auricles go on beating regularly

latter That they are not produced by variations in intraventricular pressure affecting the arterial blood column is shown by the absence of such waves in the radial pulse (Fig 3) When these waves are intrinsic in the artery they may be demonstrated in the radial pulse, as in Webster s case and in some of Gibson s cases or in the brachial pulse as in Erlanger's case

The record of the apex-beat varies in appearance in the various tracings This is due, in part, to changes which took place in the tonicity of the heart, the systolic plateau becoming better sustained as the patient improved, but in greater part to changes in the position which the patient assumed while the tracings were taken from day to day The patient suffered at first from orthopnea and had to be propped up, with the result that the heart receded from the chest wall, as improvement progressed it became possible for the patient to assume the recumbent posture without inconvenience, under such circumstances a better record of the apex-beat was obtained, as shown by the later tracings The ventricular systole is somewhat prolonged, lasting from 0 4 to 0 5 second The diastolic period is interrupted by a varying number of small waves which correspond to the *a* waves of the jugular tracing, and have the same significance The auricular contractions, which, as mentioned above, occur during the ventricular contraction, influence the form of the systolic plateau in that they deform it, usually causing a pronounced indentation or a "crushing" of its summit This effect of an auricular contraction on the form of the systolic could not serve as a reliable means of identifying an auricular systole, so that a record of the apex-beat alone can not be used for estimating the number of auricular contractions in the cardiac cycle in cases of auriculoventricular dissociation

From the time of admission (Oct 26, 1908) until November 10 following, the patient had six attacks of vertigo followed by loss of consciousness On November 10 the syncopal attacks became more frequent and were accompanied by epileptiform convulsions A number of tracings were taken on this date, but no syncopal attack occurred during the observation The analysis of the tracings, however, revealed the interesting fact that, while the auricular frequency had remained practically unchanged, the ventricular frequency had fallen considerably

TABLE 2

Date	No of Vs	Duration in 1/10 sec	No of Vs per min	No of As	Duration in 1/10 sec	No of As per min	As Vs
Nov 10, 1908	9	269	20 07	31	276	67 5	3 36 1
Nov 10, 1908	10	280	21 42	37	281	78 28	3 65 1
Nov 10, 1908	9	260	20 76	33	264	75	3 61 1
Nov 10, 1908	9	272	19 85	34	280	72 85	3 67 1
Nov 10, 1908	9	280	19 28	38	295	77 2	4 1
Nov 10, 1908	8	238	20 16	33	240	82 07	4 1
Average	—	—	20 25	—	—	75 48	3 72 1

A comparison of Table 2 with the preceding one shows that the ventricular frequency fell from an average of 33 38 per minute to an average of 20 25 per minute The auricular frequency, as stated above did

not change, so that the As Vs ratio became in consequence greater, the average being 3 72 1, instead of 2 26 · 1, as in Table 1, while in some individual tracings this ratio reached 4 1 (Fig 4) It seems as if there were some direct relation between the slowing of the ventricular contractions and the increased frequency and severity of the syncopal attacks Accordingly, this slowing of the ventricles might be regarded as the expression of a general tendency on their part to cease contracting, at least temporarily, and thereby to bring about the various nervous phenomena observed in the Adams-Stokes syndrome, through anemia of the nerve centers In this case, as in most cases so far reported, it was observed that the syncopal and epileptiform attacks were immediately preceded by a complete disappearance of the pulse for a variable period
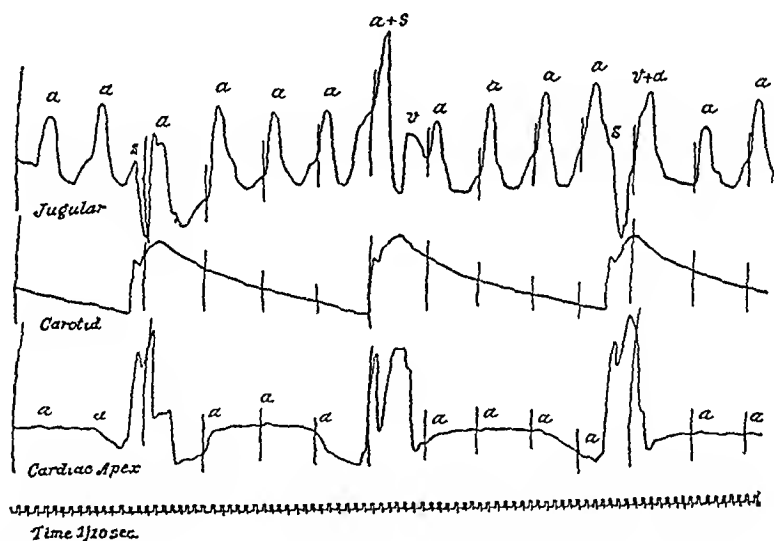
Fig 7 —Tracing taken 4 hours 30 minutes after the injection of atropin (Nov 14, 1908)

of time, usually a few seconds (4 to 8) In one instance, however, the pulse disappeared from the wrist for fully four minutes, when the patient became relaxed and was apparently lifeless Di Hull, the interne on duty, raised the foot of the bed and performed artificial respiration His efforts were rewarded by a return of the patient to consciousness, the pulse-rate rose rapidly to 120 per minute, to return shortly after to its usual low rate This increased ventricular frequency at the end of an attack, has been observed in many cases of Adams-Stokes syndrome

The presence of a complete auriculoventricular dissociation having a permanent character is strongly suggestive of an organic lesion of

the muscle bundle of His [13] Nevertheless, in order definitely to exclude the possibility of this disorder originating in some disturbance in the innervation of the heart, the atropin test was applied Dehio was the first to employ atropin as a means of determining the part played by the cardio-inhibitory apparatus in infrequent or in irregular action of the heart The same observer used the atropin test in a case of Adams-Stokes symptom-complex and found that the drug did not influence the pulse-rate in any notable manner Since then atropin has been used by a number of investigators in similar cases The effect of atropin on the heart, under such circumstances, varies with the degree of heart-block present When the block is complete, atropin causes a more or less marked increase in auricular frequency while the ventricular rate remains practically unchanged, when the block is incomplete, the increase in auricular frequency is accompanied by an increase in ven-
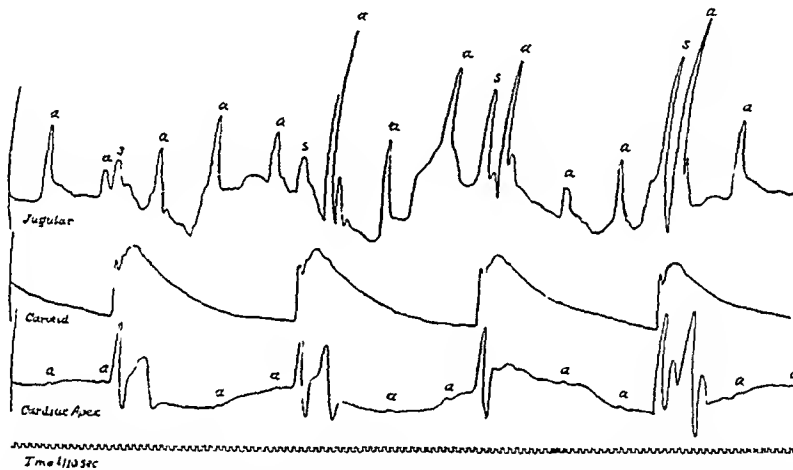
Fig 8 —Tracing taken immediately before the administration of strophanthus (Nov 20, 1908)

ticular frequency, owing to the circumstance that some of the auricular impulses are able to reach the ventricles and excite these to contraction The action of atropin in heart-block is explained by the fact, established experimentally by Erlanger and others, that the vagus nerve acts directly on the auricles only (possibly only on the right auricle), the increased ventricular (pulse) rate which normally follows the sus-

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13 Some doubt has been expressed by Kronecker and Imchanitzky concerning the generally accepted opinion that the muscle bundle of His is the pathway conducting the excitation process from auricles to ventricles, they maintain that ligation and crushing of the bundle of His proper, without including in the ligature any of the adjacent tissues, will not cause any incoordination between auricular and ventricular action (Arch internat de physiol 1906 iv, July) Paukul working in Kronecker s laboratory, has recently confirmed the findings of the above named investigators (Ztschi f Biol, 1908, li, 178 196

pension of vagus action is secondary to the increased auricular rate The presence of a complete block between auricles and ventricles naturally renders the latter absolutely independent of any change in the rate of the former

The dose of atropin ordinarily recommended for this test is 1/50 grain hypodermically, but owing to the patient's unfavorable condition it was thought safer to administer a smaller dose—viz 1/100   The results are given in Table 3

TABLE 3.—EFFECT OF ATROPIN, 1/100 GRAIN HYPODERMICALLY

Time In jection of atropin	No of Vs	Duration in 1/10 sec	No of Vs per min	No of As	Duration in 1/10 sec	No of As per min	As Vs	Remarks
Before	6	175	20 57	24	184	78 26	3 80 1	
Before	7	202	20 79	28	206	81 55	3 92 1	
Before	7	202	20 79	26	198	78 78	3 78 1	
After—								Atropin injected
Hr Min								
5	7	197	21 32	27	210	77 14	3 61 1	
8	7	192	21 87	26	205	76 09	3 48 1	
12	7	199	21 10	26	214	72 89	3 45 1	
18	6	222	16 21	33	230	86 09	5 31 1	Vs irregular
23	8	224	21 42	30	235	76 59	3 57 1	Vs regular
28	9	259	20 84	33	262	75 57	3 62 1	Vs regular
33	9	277	19 48	37	280	79 28	4 12 1	Vs irregular
37	9	280	19 28	39	289	80 96	4 2 1	Vs regular
43	9	273	19 78	37	285	77 89	3 94 1	Fig 5
48	8	248	20	37	259	85 71	4 28 1	Vs regular
58	10	246	24 39	37	250	88 8	3 64 1	Syncopal attack
1 14	8	257	18 67	39	275	85 1	4 55 1	Vs stopped 4 8 sec Fig 6
1 19	8	274	17 52	44	291	90 72	5 17 1	Syncopal attack
1 25	11	295	22 37	43	280	92 14	4 11 1	Vs stopped 4 9 sec Vs irregular
1 31	9	291	18 55	52	312	100	5 39 1	Vs regular
1 40	7	211	19 9	36	257	84 04	4 22 1	Syncopal attack Vs stopped twice, each 4 9 sec
1 46	7	216	19 44	37	230	96 52	4 96 1	Vs regular
1 53	6	184	29 34	35	218	96 33	3 28 1	Vs regular
2	7	211	19 9	38	234	97 43	4 89 1	Vs regular
4 30	9	256	21 09	40	266	90 22	4 27 1	Vs regular
4 35	8	232	20 69	32	241	79 66	3 85 1	Vs regular
4 40	8	234	20 51	34	246	82 92	4 04 1	Vs regular
4 45	8	232	20 69	36	240	90	4 35 1	Vs regular
4 50	7	219	19 17	30	229	78 6	4 1 1	Vs regular

The above analysis of the tracings shows the usual outcome of the atropin test in cases of complete heart-block—namely, acceleration of the auricles—the ventricular rate remaining unaffected   But definite conclusions from the ventricular action can not be drawn in this instance because of its irregularity during the greater part of the test   Several typical attacks occurred while the tracings were being taken   The dependence of the convulsive seizures on the cessation of the ventricular contractions is well illustrated in tracings Figures 5 and 6, where the

time of occurrence of the convulsive movements is plainly shown   It will be seen also that complete stoppage of ventricular action may occur suddenly without the preliminary gradual slowing   generally   observed (Fig 6)   Tracing Figure 5 demonstrates the increased ventricular rate which follows an attack   It is a noteworthy fact that nearly all of the instances of 'ventricular stoppage I was able to record during the observation lasted 4 9 seconds and that the prolonged stoppage seen in Figure 6 is a multiple of this (9 8 seconds)   The auricular contractions, under the influence of atropin, remained perfectly regular throughout the test with the exception noted below   The increase in rate was but slight and occurred late—much later than has been observed heretofore   It is probable that the smallness of the dose of atropin employed,
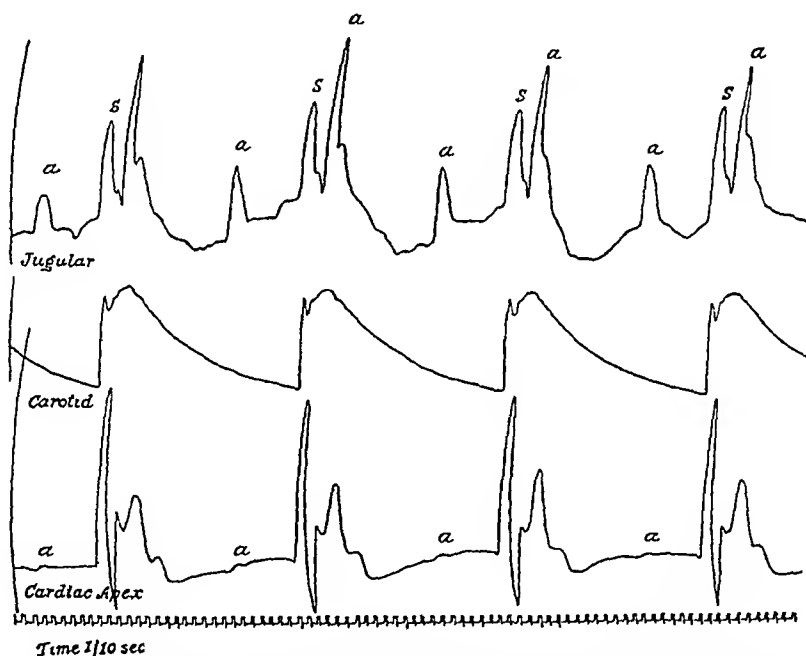
Fig 9 —Tracing showing the effect of strophanthus   The auricular contractions have decreased, the ventricular contractions have increased in frequency (Nov 23, 1908)

as well as the sluggish state of the patient's circulation, are the factors responsible for this slight and slow response   There does not seem to be any relation between the stoppage of the ventricles which precedes an attack and the frequency of the auricular contractions   Erlanger states that in the case he studied the slowing of the ventricles was synchronous with a sudden acceleration of the auricles   I was unable to confirm this observation in the case under discussion   The auricular rate, it is true, increased under the influence of atropin, this increase, however, was not a sudden but a gradual one, and the observation made by Erlanger that atropin will not call forth an attack is attributed by him

to this circumstance   The only thing of note in this connection is a
slight and momentary auricular arrhythmia which took place during a
mild attack (Fig 5)   This is the only instance in which this was
observed and may have been, therefore, nothing but a coincidence   The
complete dissociation of the action of auricles and ventricles, together
with the results of the atropin test, indicate that the break in the con-
ducting path between auricles and ventricles is complete and consti-
tutes strong presumptive evidence of an organic lesion implicating the
bundle of His to a marked extent   An opportunity is thereby made
available for the study of drugs used in cardiac therapeutics, about whose
mode of action there may still be some doubt   Such a drug is strophan-
thus   Germain Sée and Gley, Delseaux[14] and other pharmacologists are
of the opinion that strophanthus does not modify the cardiac rhythm
through any action on the medulla or on the cardiac nerves   On the
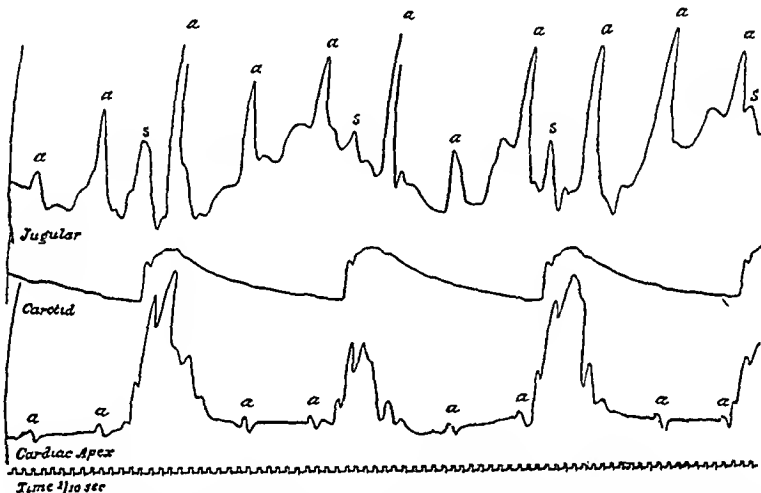
Fig 10 —Tracing taken after the withdrawal of strophanthus   Note the re-
turn of auricular contractions to their former rate   The action of the entire
heart has increased in strength as shown by the increased height of the auricular
and ventricular contractions (Dec 29, 1908)

other hand, Kochmann[15] observed that, after section of both vagi, stro-
phanthin (Merck) did no longer diminish the rate of the heart-beat
Liagre[16] was able to fully confirm these latter findings with both the
tincture of strophanthus and strophanthin   He found, also that these
preparations will fail to slow the heart's action when the vagi have
had their conductivity suspended by means of atropin   He demon-

14 Sée, Germain, and Gley and Delseaux (quoted by Liagre)   Jour de physiol
et de path gén, 1906, viii, 988)
15 Kochmann   Beitrag sur Wirkung einiger Korper der Digitalisgruppe auf
den N Vagus Arch internat de pharmocod, 1906, xvi, 221
16 Liagre, C   Action de la teinture de strophantus et de la strophantine sur
le rhythme du cœur   Jour de physiol et de path gén, 1906, viii, 988

stiated, furthermoie, that strophanthus, or its alkaloid, does not pioduce any bradycardia in the perfused and isolated heart, but that, on the contiary, a noticeable tachycardia ensues which, if the dose be too laige is complicated by arrhythmia

In a previous communication[12] I showed that strophanthus given in medicinal doses, in a case of complete heart-block, decreases the auriculai iate, while the ventricular rate remains practically constant   The action of the drug was also studied in this case   Five minims of the tincture of strophanthus (U S P) was given three times a day fiom November 21 till November 25, on which date the dose was increased to ten minims   The administration of the drug was continued at this dose till Dec 7, 1908, when it was withdrawn altogether   Tracings weie taken just before the administration of strophanthus and then afteiward, sufficiently often to determine the reaction of the heait toward the drug, the observations were continued after its withdrawal The results aie presented in Table 4, and are also graphically represented in a chart (Fig 12)

TABLE 4 —EFFECT OF STROPHANTHUS

Date	No of Vs	Duiation in 1/10 sec	No of Vs per min	No of As	Duration in 1/10 sec	No of As pei min	As Vs		Remarks
11/20, '08	8	207	23 18	25	204	73 52	3 15	1	
	8	203	23 64	26	219	71 23	3 01	1	
	8	201	23 88	26	214	72 89	3 05	1	Before
	9	238	23 68	28	235	71 48	3 15	1	
11/21, '08	—	—	—	—	—	—	—		Strophanthus m v ti d
11/22, '08	26	681	22 9	78	729	64 19	2 8	1	Strophanthus m v ti d
11/23, '08	55	1208	2l 31	116	1271	54 76	2	1	Strophanthus m v ti d
11/25, '08	55	1477	22 34	180	1535	70 35	3 14	1	Strophanthus m ᴠ ti d
11/26, '08	31	592	31 41	64	600	64	2 03	1	Strophanthus m ᴠ ti d
11/27, '08	22	399	33 08	46	417	66 18	2 00	1	Strophanthus m ᴠ ti d
11/28, '08	48	904	31 85	88	938	56 29	1 45	1	Strophanthus m ᴠ ti d
11/29, '08	30	619	29 07	61	636	57 54	2 2	1	Strophanthus m ᴠ ti d
11/30, '08	34	72S	28 02	74	753	58 96	2 1	1	Strophanthus m ᴠ ti d
12/2, '08	25	512	29 29	56	521	64 49	1 98	1	Strophanthus m ᴠ ti d
12/5, '08	38	794	28 71	90	807	66 91	2 33	1	Strophanthus m ᴠ ti d
12/7, '08	40	836	28 7	93	879	63 4S	2 21	1	Strophanthus stopped
12/9, '08	30	636	28 3	S1	701	69 32	2 44	1	
12/11, '08	30	664	27 1	78	6S0	68 S	2 53	1	
12/13, '08	36	774	27 9	97	817	71 23	2 55	1	
12/15, '08	58	1234	28 2	175	1308	80 27	2 84	1	
12/17, '08	62	105S	29 53	138	1113	74 39	2 51	1	
12/19, '08	4S	1016	28 34	128	1070	71 77	2 53	1	
12/20, 0S	34	692	29 47	100	720	83 33	2 S2	1	Gone home for Christmas
12/27, '0S	44	989	26 69	137	1073	76 6	2 S6	1	
12/29, '0S	42	SS7	28 41	131	96S	S1 2	2 S5	1	
12/31, '0S	52	1032	30 23	162	1102	SS 2	2 91	1	
1/2, '09	52	1151	27 1	155	122S	75 73	2 S	1	
1/4, '09	43	910	28 35	135	960	S4 37	2 97	1	
1/6, 09	45	963	28 03	151	1020	SS SS	3 17	1	Six groups of 4 1 ratio
1/S, 09	54	1123	2S S5	156	1157	S0 9	2 S	1	
1/10, 09	42	926	27 21	135	992	S1 65	3	1	

The most striking effect of the action of strophanthus on the heart's action is seen in the notable decrease in the frequency of the auricular contractions   It is to be noted that no such effect is exerted upon the ventricular contractions, on the contrary, these are conspicuously increased in rate   In this way is brought about an approximation toward normal heart action, as shown by the decrease in the As Vs ratio   These findings are a confirmation of the statement I made in another place, that strophanthus slows the heart by stimulating the vagus nerve   They also confirm the animal experiments of Kochmann and of Liagre and show the propriety of their application to the human heart   The ventricles in this case exhibit the tendency to acceleration manifested in the tachycardia of the isolated and perfused heart when it is subjected to the action of strophanthus   Von Tabora[17] made some experiments on the mammalian heart which may be of interest in this
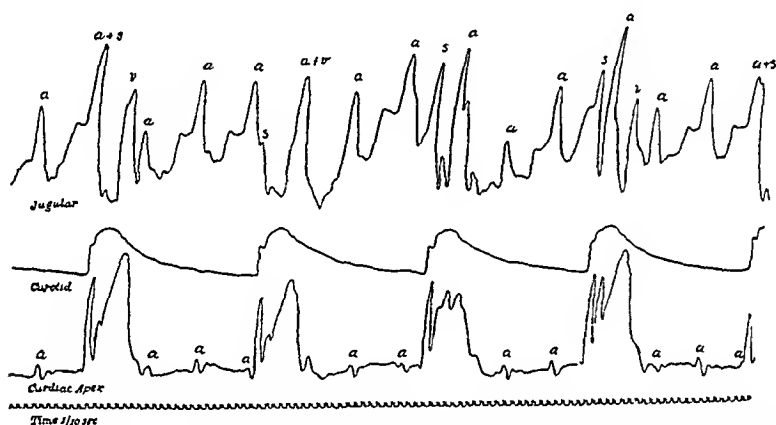
Fig 11 —Tracing taken later after the withdrawal of strophanthus   The auricular frequency continues to increase   The improved cardiac condition persists (Jan 6, 1909)

connection   After crushing the bundle of His, thereby producing a complete and permanent auriculoventricular dissociation, this investigator injected digitalin intravenously, the results which he obtained were a doubling of the ventricular rate and a gradual decrease in the auricular rate going on to complete arrest   Thus it will be observed that there exists a certain parallelism in the mode of action of strophanthus and digitalis (digitalin) in bringing about a decrease in the frequency of the heart beat

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17 Von Tabora, D   Ueber die experimentelle Erzeugung von Kammersystolenausfall und Dissociation durch Digitalis   Ztschr f exper Path u Therap, 1906, iii, 549

That the slowing of the auricles was not fortuitous is shown by the fact that, following the complete withdrawal of the drug, their rate gradually increased until it reached and went beyond the figure which it had before the test   The tonic action of the drug on the ventricles persisted, so that their frequency remained a little higher than immediately before the test

The improvement of the circulation under the influence of strophanthus had a most remarkable result   The syncopal and epileptiform seizures which had been increasing in frequency and severity gradually became less frequent and in a short time disappeared, not to return
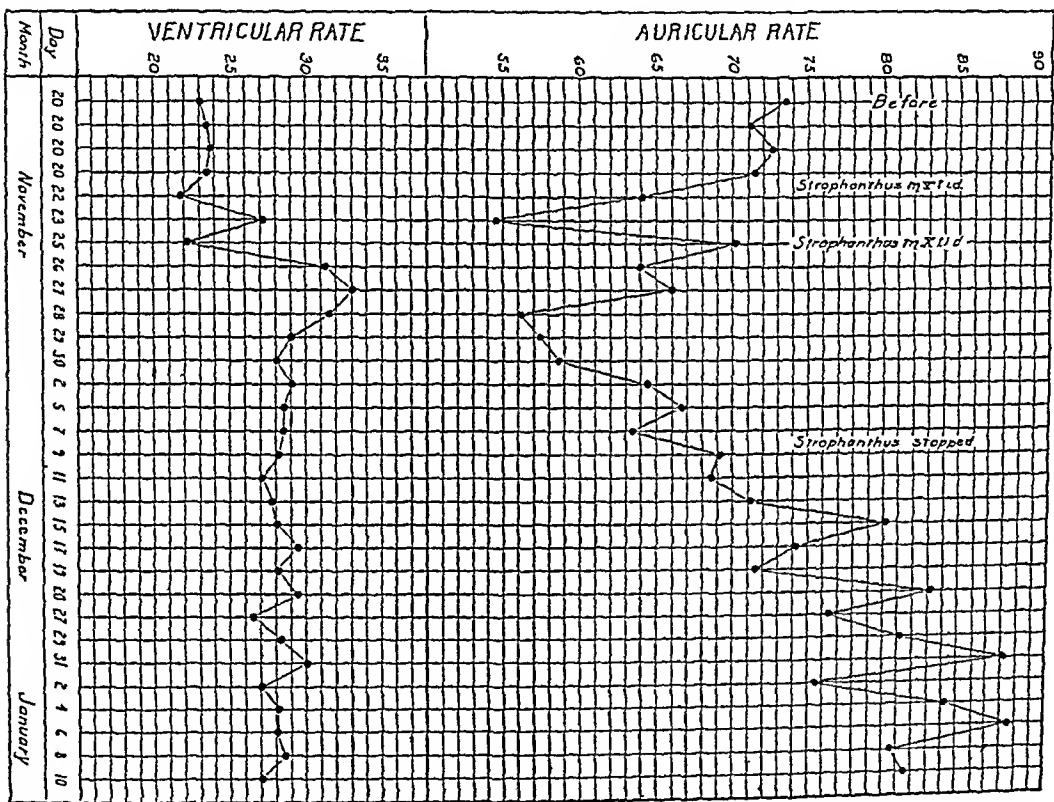
Fig 12 —Chart based on Table 4, showing the effect of strophanthus on the auricular and ventricular rates   Apparently, the auricles either escape from vagus stimulation or the vagus ultimately fails to respond to the prolonged action of the drug

again, even after the withdrawal of the drug   The patient ultimately felt so well that he left the hospital

Jagic[18] has reported a case of Adams-Stokes syndrome in which a temporary improvement followed the administration of small doses of digitalis (0 05 gm a day)   He supposes that this result was an effect

18 Jagic, N   Ein Beitrag zur Kasuistik des Adams Stokes schen Symptomen komplexes   Ztschr f klin , Med , 1908, kvi

of the small dose of digitalis used, which, he thinks, could hardly have stimulated the vagus, but could, nevertheless, have acted directly on the heart muscle [19] He states that digitalis in larger doses may do harm by further depressing conduction through vagus stimulation, but, as his case was in all probability one of complete heart-block, and as Erlanger's experiments, as well as the atropin and strophanthus tests, indicate that the vagus influences the auricle only, Jagic's fears do not appear well founded   That vagus stimulation, in cases of complete block, is not incompatible with decided improvement in ventricular action is shown in the study of the effect of strophanthus herein reported   The result might be different in cases of incomplete heart-block, for in this condition some of the auricular impulses pass over to the ventricles, and usually these are still dependent for their contraction on the arrival of the auricular impulses   A slowing of the auricles, through the action of digitalis or strophanthus on the vagus, would inevitably be followed by a decrease in the frequency of the ventricular contractions   Digitalis might, moreover, further depress the conductivity of the auriculoventricular bundle   The combination of these two effects would naturally aggravate the condition   Such a result is apparently not to be feared in cases of complete heart-block

I wish here to express my indebtedness to Professor J C Wilson for the privilege of studying the case

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19 The article does not contain any tracings, nor is there any mention of any having been taken

EFFECTS OF THE ADMINISTRATION OR THE WITHHOLDING OF IODIN-CONTAINING COMPOUNDS IN NORMAL, COLLOID OR ACTIVELY HYPERPLASTIC (PARENCHYMATOUS) THYROIDS OF DOGS

SOME EXPERIMENTS ON (CONGENITAL) PRENATAL THYROID HYPERPLASIA IN DOGS, REMARKS ON THE CLINICAL MANIFESTATIONS ASSOCIATED WITH MARKED THYROID HYPERPLASIA `

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The observations and experiments here recorded have been made on dogs, and include three with normal, eight with colloid and seventeen with actively hyperplastic glands, as ascertained by the first specimen of thyroid removed The plan followed has been to remove a control portion of the thyroid from each dog for histologic diagnosis and iodin determination, and at intervals to remove other portions for comparison

Our experiments may be divided into two groups (1) those in which iodin was administered and (2) those in which no iodin was administered, except what was contained in a liberal diet of cooked meat, bread, sodium chlorid, milk and water The food being the same in each group, no other remarks are necessary, except that dogs normally store some iodin from such a diet These two groups have been tabulated, and in presenting Tables 1 and 2 we have arranged the cases according to the anatomic groups represented, as ascertained by the histologic diagnosis of the first specimen of thyroid removed Thus normal and colloid glands are placed first, then follow in order the several degrees of hyperplasia

We shall discuss the cases according to the groups represented

1 *Normal Glands* —Of the three subjects (A-123, A-26, A-27), only one (A-26) was given iodin directly In this case the iodin was distinctly but not markedly increased in the remaining lobe This lobe also increased in size, but remained normal in structure The other two subjects (A-123 and A-27) showed hyperplasia of the remaining lobes These three cases show that iodin does have a preventive effect on the

hyperplasia and also that iodin is increased even in normal glands, though slightly This is what is expected when one recalls the normally wide variations in the iodin contents of normal glands from all animals[1] The other point of importance, namely, that glands may grow in size and yet never show any deviation from normal structure, is of considerable interest, in that it furnishes additional proof that hyperplasia, however slight, is no part of the normal growth of normal glands, but must be the evidence of some abnormal factor or stimulus Further, it shows that the administration of iodin will not prevent the normal growth of a normal gland Lastly, when the three cases are taken together, it is seen that the amount of thyroid removed is of secondary importance to the iodin content in determining the occurrence of hyperplasia, although iodin does not seem to prevent hyperplasia after a certain maximum of thyroid is removed, just as it does not prevent the normal growth of pups' thyroids It will be noted that all three dogs were young This, as Horsley[2] and all subsequent investigators have shown, is very important, since the needs for the gland's activities are greater in youth The symptoms following the removal of the thyroid are also greater, and compensatory hyperplasia occurs more constantly and more rapidly the younger the animals are

Colloid Glands —There were three cases (A-51, A-120, A-118) in which iodin was given and five cases (A-63, A-95, A-104, A-106, A-122) in which it was not given In the five cases in which iodin was not given there was a gradual lessening of iodin in the succeeding portions removed, just as in the normal glands This is in sharp contrast with the hyperplasias, all of which will be seen to have gained slightly in iodin It suggests that the ability of normal or colloid glands to store iodin from the food is much less than that of actively hyperplastic glands While in general the iodin contents of colloid glands per gram are less than those of normal glands per gram, this is not necessarily true The three glands in which iodin was administred show a marked increase in the thyroid iodin, though, as will be seen, it is not as great as that which occurs in the active hyperplasias, thus agreeing with the normal glands in this respect In two of the cases, A-104 and A-106, secondary (i e, glands undergoing active hyperplasia for the second time) compensatory hyperplasia occurred, but only after the iodin had been greatly reduced This also is in harmony with what nor-

1 Marine and Lenhart Further observations on the relation of iodin to the structure of the thyroid gland in the sheep, dog, hog and ox THE ARCHIVES INT MED, 1909, iii, 66
2 Horsley Brit Med Jour, 1892, i, 215

mally occurs in the spontaneous secondary hyperplasias In the case of colloid glands, just as was shown for normal glands, the amount of gland removed does not seem to be so important as is the iodin content in starting the hyperplasia and, also just as in the normal glands, there is a level below which iodin will not protect against secondary hyperplasia All the evidence taken together indicates that colloid glands behave exactly as normal glands when subjected to the same experiments, or, in other words, that colloid glands parallel normal glands

Hyperplasias—Discussing the six cases in which no iodin was directly administered, it will be seen that they represent degrees of hyperplasia from *early* to *moderate* They all show an increase of iodin in the successive portions removed This is in sharp contrast with the normal and colloid glands, which under-the same conditions of food and experiment did *not* show increases of iodin Associated with this slight gradual increase in iodin, there is a slow return toward colloid glands This slow return toward the colloid condition should be contrasted with the rapid return to the colloid condition in those cases given iodin directly

Taking up the cases of hyperplasia in which iodin was administered, there were eleven, ranging from *normal early* to *marked* glandular hyperplasia In all these cases very marked and very rapid increases in the iodin contents are shown Taking the whole series, the general impression is that iodin is stored more rapidly in the cases with marked hyperplasia This is very evident when colloids or normals are contrasted with the hyperplasias The form of administration of iodin appears to be of less importance than the degree of hyperplasia in determining the rapidity with which iodin is taken up by the thyroid The amount of iodin taken up obviously must depend on the quantity administered, the degree of hyperplasia and the extent of the epithelial surface The rapidity of the involution (reversion) process in subjects given iodin may be judged from A-119 in which noticeable histologic differences were present in five days This is about the average time required, though we have seen it in three days The average time required to induce complete involution (reversion) may also be ascertained from this case, in which in 26 days the entire series of changes from marked glandular hyperplasia back to pure colloid gland occurred How much this may be modified by different methods of administration and different preparations of iodin is yet to be ascertained Our data indicate that these will be found to be of minor general pharmacologic importance though probably of great therapeutic importance Desiccated thyroid preparations appear to have no advantage over the inorganic

TABLE 1—EXPERIMENTS IN

Case No	Sex	Age	Weight Kg	Day, Month, Year of Operation	Part Removed	Weight of Thyroid Removed, gm	Color	Consist ency	Visible Colloid	Histologic Diagnosis
A-26a	F	3 mos	2 4	15, 2, '07	R lobe	0 24	Reddish, transl	Firm	Normal	Normal
A-26b	F	4½ mos	4 0	2, 4, '07	L lobe	0 305	Yellow, transl	Firm	Normal	Normal
A-51a	M	Middle	3 2	29, 3, '07	L lobe	22 1	Reddish, transl	Moderate	Reduc'd	Colloid
A 51b	M	Middle	3 0	4, 4, '07	R lobe	23 1	Reddish, transl	Moderate	Normal	Colloid
A 120a	M	7 mos	3 6	15, 4, '08	L lobe	1 7	Yellow, transl	Firm	Normal	Colloid
A-120b	M	7½ mos	3 2	2, 5, '08	R lobe	1 1	Yellow, transl	Firm	Normal	Colloid
A-118a	M	3 yrs	9 0	25, 3, '08	Part of 1 lobe	2 7	Yellow, transl	Firm	Normal	Colloid
A-118b	M	3 yrs	9 0	30, 3, '08	Part of 1 lobe	6 5	Yellow, transl	Firm	Normal	Colloid
A-118c	M	3 yrs	?	4, 4, '08	Part of 1 lobe	6 0	Yellow, transl	Firm	Normal	Colloid
A 118d	M	3 yrs	?	10, 4, '08	Part of r lobe	8 25	Yellow, transl	Firm	Normal	Colloid
A 118e	M	3 yrs	?	15, 4, '08	Part of r lobe	7 3	Yellow, transl	Firm	Normal	Colloid
A-118f	M	3 yrs	?	6, 5, '08	Part of r lobe	3 3	Reddish, transl	Moderate	Visible	Colloid
A-118g	M	3 yrs	?	8, 5, '08	Part of r lobe	3 25	Reddish, transl	Moderate	Visible	Colloid early
A-17a	F	Middle	5 4	22, 1, '07	R lobe	0 7	Gray, transl	Firm	Normal	Normal early
A-17b	F	Middle	5 0	15, 3, '07	L lobe	0 65	Clear, transl	Firm	Normal	Colloid
A 18a	F	Middle	5 4	22, 1, '07	L lobe	7 5	Grayish, opaque	Soft	None	Mod gland hyperplasia
A-18b	F	Middle	3 18	11, 2, '07	R lobe	4 75	Yellow, transl	Firm	Normal	Colloid
A-73a	M	Young	8 6	25, 4, '07	L lobe	2 6	Reddish, opaque	Moderate	None	Moderate gland hyperplasia
A-73b	M	Young	7 1	4, 5, '07	R lobe	2 1	Reddish, transl	Firm	Reduc'd	Colloid early gland
A-16a	M	Old	5 0	22, 1, '07	L lobe	4 15	Grayish, opaque	Soft	None	Mod marked gland hyperp
A-16b	M	Old	3 2	20, 2, '07	R lobe	2 7	Yellow, transl	Firm	Normal	Colloid
A-52a	F	Pup	2 7	29, 3, '07	R lobe	3 6	Grayish, opaque	Soft	None	Mod marked gland
A 52b	F	Pup	2 8	22, 4, '07	L lobe	2 0	Clear, transl	Firm	Normal	Colloid
A 55a	M	Pup	7 27	1, 4, '06	L lobe	72 0	Opaque	Soft	None	Mod marked gland hyperp
A 55b	M	Pup	6 36	8, 4, '09	R lobe	57 2	Gray red, opaque	Soft	None	Moderate gland hyperplasia
A-125a	M	1 yr	6 8	9, 5, '08	Part of 1 lobe	5 8	Grayish, opaque	Soft	None	Marked gland hyperplasia
A 125b	M	1 yr	6 8	18, 5, '08	Rem of 1 lobe R lobe	93 0 95 0	Grayish, opaque	Soft	None	Moderate marked gland hyperplasia
A 114a	F	8 mos	5 9	19, 2, '09	Part of 1 lobe	116	Grayish red, opaque	Soft	None	Marked gland hyperplasia
A-114a'	F	8 mos	5 9	19, 2, '08	Accessory thyroid	5 0	Grayish-red, opaque	Soft	None	Marked gland hyperplasia
A 114b	F	8 mos	5 0	24, 2, '08	L lobe	27 2	Grayish red, opaque	Soft	None	Mod marked gland hyper plasia
A-114c	F	8 mos	4 2	26, 2 08	R lobe entire	23 25	Yellowish, opaque	Soft	Visible	Colloid, mod gland hyperp

Iodin, per gm, Dried	Iodin, per gm, Moist	Amount, Form and Duration of Iodid Administration	Complicating Factors During Experiment	Remarks
2 300	0 380		None	
3 467	0 705	1 c c sat alc sol iodid from 2, 21 to 3, 8, '07	None	Chloroformed to death 4, 2, '07
0 707	0 138		None	
0 969	0 245	6 5 gr tablets desiccated thyroid from 3, 29 to 4, 3, '07	Pneumonia	Death on 5th day of pneumonia
2 353	0 400	Distemper and chorea on admission *		
4 480	1 195	Given 70 gtt syrup of ferr iodid from Apr 16 to May 2		No apparent improvement in distemper and chorea, chloformed to death 5, 2, '08
0 721	0 186		None	
1 000	0 237	Given 7 5 gm of desiccated thyroid containing 1 092 mg per gm dried	None	
0 477	0 106*	7 5 gm desiccated thyroid iodid assign'd as above since last opr	Slight wound infection, HgCl2 dressing	Iodin determination uncertain owing to presence of mercury *
1 815	0 487	120 gtt syr ferr iodid since last operation	Infection cleared up	
1 146	0 227	120 gtt syr ferr iodid since last operation	None	
0 893	0 171	160 gtt syr ferr iodid from 4, 16, to 5, 1	None	
0 126	0 026	No iodid since last operation	Tetany	Died 2 days after last operation of tetany
*			None	Iodin not determined — accident — bitch pregnant *
4 615	1 093	200 mg iodid given from 1, 26 to 2, 7, '07	None	Killed with chloroform 3, 15, '07
0 261	0 056		None	
4 184	1 265	Fed 545 gms fresh sheep's thyroid from Jan 25 to Feb 3	Emaciation, diarrhea	Dog died after great loss of weight, associated with serious diarrhea
0 420	0 071		Canine chorea, "distemper"	
*		5 gtt sat alc iodin from 4, 26 to 4, 30	Acute distemper	No iodin determination, specimen lost
0 086	0 014		None	
1 739	0 393	Fed 65 5 gr tablets in 28 days following 1st operation	Emaciation	Killed with chloroform 2, 20, '07, great loss of weight, slight diarrhea
0 413	0 057		None	
3 196	0 815	15 gtt sat alc sol iodin from 4, 1 to 4, 11	None	Killed with chloroform
0 054	0 008		None	
1 399	0 292	7 gtt sat alc sol of iodin since April 2	Pulmonary embolism	Dog died suddenly night of April 8, and autopsy showed the pulmonary artery plugged with an embolus
0 077	0 016		None	
2 107	0 453	Wound packed 6 times with iodoform gauze	Wound infection	Died suddenly May 18, owing to wound being torn open by another dog in a fight *
0 000	0 000		None	Dog was emaciated, pulse 180, heart action shook entire body, slight diarrhea
0 000	0 000		None	
1 123	0 243	120 gtt syr ferr iodid fed from 2, 19 to 2, 24	Slight wound infection	
1 480	0 352	40 gtt syr ferr iodin in 2 days	Fatal hemorrhage	Hemorrhage due to infected silk ligature

TABLE 1 —EXPERIMENTS IN

Case No	Sex	Age	Weight Kg	Day, Month Year of Operating	Part Removed	Weight of Thyroid Removed gm	Color	Consistency	Visible Colloid	Histologic Diagnosis
A-116a	F	7 mos	6 5	13, 3, '08	R lobe	6 5	Grayish, opaque	Soft	None	Marked gland hyperplasia
A-116b	F	7 mos	6 0	17, 3, '08	R lobe	11 6	Grayish, opaque	Soft	Visible	Colloid mod marked gland hyperplasia
A-116c	F	7 mos	5 5	21, 3, '08	R lobe	27 6	Yellowish opaque	Firm	Visible	Colloid mod marked gland hyperplasia
A-116d	F	7 mos	5 5	24, 3, '08	L lobe	43 5	Yellowish, opaque	Firm	Visible	Colloid early gland hyperplasia
A-117a	M	2 yrs	6 9	21, 3, '08	R lobe	4 2	Gray red, opaque	Soft	None	Marked gland hyperplasia
A-117b	M	2 yrs	6 6	25, 3, '08	L lobe ⎰ R lobe ⎱	67 10	Yellowish opaque	Soft	Just visible	Colloid mod marked
A-119a	M	8 mos	8 4	10, 4, '08	L lobe	9 82	Reddish, opaque	Soft	None	Marked gland hyperplasia
A-119b	M	8 mos	8 2	15, 4, '08	L lobe	20 5	Yellowish red, opaque	Soft	Just visible	Colloid mod marked gland
A-119c	M	8 mos	8 0	22, 4, '08	R lobe	1 5	Yellowish, opaque	Moderate	Visible	Colloid mod gland
A-119d	M	8 mos	10 0	28, 4, '08	R lobe	7 2	Yellowish, transl	Firm	Normal	Colloid early gland
A-119e	M	9 mos	10 5	6, 5, '08	R lobe	6 5	Yellow, transl	Firm	Normal	Colloid
A-119f	M	10 mos	11 9	15, 6, '08	Remand'r of lobes	1 3	Yellow, transl	Firm	Normal	Colloid

salts of iodin, or over pure iodin, in inducing these histologic changes If anything, the pure iodin is taken up more rapidly   Going back to the cases in which iodin was not administered, it will be seen that in sharp contrast with A-119, in which complete involution (reversion) occurred in twenty-six days, A-121 did not reach complete involution (reversion) for sixty-six days

FORMS, MODE OF ADMINISTRATION AND AMOUNTS OF IODIN ADMINISTERED

We have employed iodoform, fresh sheep's thyroids, desiccated sheep's thyroid, pure iodin, ferrous iodid, all of which forms are followed by the storage of iodin in the glands, whether normals, colloids or hyperplasias   The resulting histologic effect in all is the same, viz   the return to the colloid or quiescent condition

As to the mode of administration   It is taken up by the thyroid when "painted" on the skin, given by mouth or injected hypodermically On this point, however, we do not possess sufficient data to differentiate specifically between the several modes of administration other than that pure iodin apparently is taken up most rapidly

WHICH IODIN WAS GIVEN—Continued

Iodid, per gm, Dried	Iodid, per gm, Moist	Amount, Form and Duration of Iodid Administration	Complicating Factors During Experiment	Remarks
0 015	0 003	No iodin administered prior to first operation	None	Rhachitic, anemic and somewhat emaciated, with forcible action and pulse 160, eyes weeping and stools soft
1 000	0 188	120 gtt syr ferr iodid in 4 days since first operation	Slight wound infection	
2 153	0 477	120 gtt syr ferr iodid in 4 days since 2d operation	Slight wound infection	
2 691	0 693	80 gtt syr ferr iodid in 3 days	Fatal hemorrhage	Hemorrhage due to infected ligature sloughing off a large vein, thymus atrophic, spleen and lymph gland enlarged
0 065	0 014	No iodin given prior to 1st operation	None	
2 384	0 540	120 gtt syr ferr iodid given in 4 days since 1st operation	Over anesthetized	Ineffectual efforts at resuscitation
0 200	0 040	No iodin given prior to 1st operation	None	Anemic, but fat deposits normal
2 861	0 553	120 gtt syr ferr iodid in 5 days since first operation	None	
4 078	0 860	300 gtt syr ferr iodid in 7 dys since 2d ope	None	
3 353	0 749	No iodin given since last operation	None	Dog gaining weight rapidly
3 522	0 894	No iodin given	None	
2 770	0 554	No iodin given	Killed by negligent anesthetist	An attempt was made June 1, but no thyroid found in a hasty exam Dog killed June 15 by negligence after operation was completed

Coming to the amounts of iodin administered, one of the most striking things brought out is that of the minute amounts (minute in contrast with what we had generally seen recommended in the treatment of goiter) necessary to induce thyroid changes It appears that the more marked the hyperplasia the greater is the amount of iodin taken up, since in normal dogs one can give very large amounts of iodin without inducing any systemic effect or raising the iodin content of the glands any more than much smaller doses do in actively hyperplastic glands It may be well to refer to the systemic effects produced by iodin as we have seen them

In the first place, reference to Tables 1 and 2 will show that in normal or colloid glands there is either little change in body weight or there is about the same change whether iodin was administered or not This is not true of the subjects with hyperplasia All such subjects when fed iodin lost weight rapidly for a time (one to two weeks), then started to gain, while in those not fed iodin a loss of weight was not observed We have made some specific experiments regarding the loss of weight Thus we took three markedly goitrous pups of the same litter aged six

TABLE 2—Experiments in which

Case No	Sex	Age	Weight	Day, Month, Year of Operation	Part Removed	Weight of Gland Removed	Color	Consistency	Colloid
A 27a	F	3 mos	1 85	15, 2, '07	R lobe	0 15	Reddish, transl	Firm	Normal
A-27b	F	3 mos	1 53	2, 4, '07	L lobe	0 15	Reddish, transl	Firm	Reduced
A-123a	M	52 days	1 4	7, 5, '08	L lobe	0 195	Reddish, transl	Firm	Normal
A-123b	M	3½ mos	2 5	1, 6, '08	One half of r lobe	0 100	Reddish, transl	Firm	Normal
A-123c	M	8⅔ mos	8 1	7, 12, '08	All of r lobe	0 600	Gray, red	Moderate	None
A-63a	F	Middle *	12 7	17, 4, '07	L lobe	14 25	Yellowish, transl	Firm	Normal
A-63b	F	Middle	12 7	22, 5, '07	R lobe	14 00	Yellowish, transl	Firm	Normal
A-95a	F	Middle	5 9	11, 5, '07	L lobe	5 1	Yellowish, transl	Firm	Normal
A-95b	F	Middle	5 7	6, 6, '07	R lobe	3 4	Yellowish, transl	Firm	Normal
A-104a	F	Middle	7 71	10, 9, '07	R lobe ⅔ l lobe	1 7 1 45	Yellowish, transl	Firm	Normal
A-104b	F	Middle	7 7	4, 1, '08	Part of l lobe	2 25	Reddish, transl	Firm	Visible
A-104c	F	Middle	7 7	7, 1, '08	Remains of l lobe	0 230	Reddish, transl	Firm	Visible
A-106a	F	Middle	11 8	5, 6, '07	R lobe	29 5	Clear, brownish yellow	Firm	Normal
A-106b	F	Middle	9 52	15, 7, '07	½ l lobe	15 0	Clear, brownish yellow	Firm	Normal
A-106c	F	Middle	9 50	10, 9, '07	½ of remaining part of l lobe	3 0	Reddish, yellow	Moderate	Reduced
A-106d	F	Middle		7, 12, '07	Remains of l lobe	4 5	Reddish, opaque	Soft	Just visible
A-122a	F	2 mos	1 8	7, 5, '08	Part of l lobe	2 2	Yellow, transl	Firm	Normal
A-122b	F			21, 5, '08	Part of l lobe	2 5	Yellow transl	Firm	Normal
A-122c	F		2 3	1, 6, '08	Part of l lobe	1 0	Yellow, transl	Firm	Normal
A-122d	F			12, 6, '08	Part of l lobe	1 8	Yellow, transl	Firm	Normal
A-122e	F	3 mos	2 9	17, 6, '08	Entire r lobe	10 5	Yellow, transl	Firm	Normal
A-64a	M	Pup	2 9	17, 4, '07	L lobe	2 25	Reddish, opaque	Moderate	Reduced
A-64b	M		4 1	5, 6, '07	R lobe	2 3	Reddish, transl	Firm	Normal
A-94a	F	Middle	2 15	11, 5, '07	L lobe	1 5	Reddish, transl	Firm	Normal
A 94b	F	Middle	1 95	25, 5, '07	R lobe	1 0	Reddish, transl	Firm	Normal
A-112a	F	Young adult	5 4	15, 1, '08	L lobe and ⅔ of r lobe	4 15	Reddish, transl	Moderate	Reduced
A-112b	F	Young adult	5 4	25, 3, '08	Part of r lobe	?	Reddish transl	Firm	Normal
A-112c	F	Young adult	5 9	7, 12, '08	All of r lobe	0 250	Reddish opaque	Moderate	Visible
A-74a	F	Young	5 44	25, 4, '07	L lobe	3 6	Reddish, opaque	Moderate	Reduced
A-74b	F	Young	6 35	1, 6, '07	R lobe	2 8	Reddish, opaque	Moderate	Reduced
A-126a	M		?	2, 6, '08	L lobe 5/6 r lobe	13 0 12 8	Reddish, transl	Moderate	Visible
A-126b	M	2 years	?	29, 6, '08	Remains of r lobe	3 3	Reddish brown	Moderate	Visible

IODIN WAS NOT GIVEN

Histologic Diagnosis	Iodin per gm, dried	Iodin per gm, Moist	Complicating Factors in Experiment	Remarks
Normal	0 886	0 248	None	
Early gland hyperplasia	1 520	0 253	Pneumonia	
Normal	6 921	1 384	None	
Normal			None	
Marked gland hyperplasia	0 115	0 025	None	
Colloid	1 246	0 298	None	*
Colloid	0 323	0 092	None	Killed 5, 22, '07
Colloid	1 076	0 251	None	
Colloid	0 719	0 163	None	Killed with chloroform 6, 6, '07
Colloid	2 738	0 510	None	Bitch gave birth to 5 pups 5, 17, '07 Impregnated again 9, 7 '07
Colloid, early gland				
Colloid, early gland			Tetany	Died 1, 7, '07 of tetany
Colloid	0 308	0 083	None	
Colloid	0 554	0 066	None	
Colloid, mod gland hyperplasia	0 554	0 099	None	
Colloid, mod gland hyperplasia	0 115	0 022	Probably myxedema	Bitch died 1, 21, '08—1½ months after last operation Accessory thyroids present
Colloid	1 520	0 370	None	On admission neck brown from iodin
Colloid	1 350	0 384	None	
Colloid	1 621	0 437	None	
Colloid	1 262	0 350	None	
Colloid, gland	1 615	0 361	None	Killed June 17 by another dog, neck terribly torn and r thyroid lobe hanging from wound *
Early gland hyperplasia	0 300	0 051	None	
Colloid	2 326	0 451	None	Killed with chloroform 6, 6, '07
Early gland hyperplasia	0 657	0 122	None	
Early gland hyperplasia	1 024	0 215	HgCl₂ poisoning	Died May 25 of acute HgCl₂ poisoning
Early mod gland hyperplasia	0 332	0 078	Pregnant	
Colloid			Pregnant	Gave birth to 2 pups 3, 15, '08 Gave birth to 5 pups 10, 29 '08
Colloid, mod marked gland hyperplasia	0 128	0 030	None	Tetany developed during second pregnancy, controlled by CaCl₂, developed myxedema after last operation
Mod gland hyperplasia	0 521	0 072	None	
Colloid, early gland hyperplasia	1 452	0 275	None	Killed with chloroform 6, 1 '07
Colloid mod gland hyperplasia	0 448	0 098	None	
Colloid, early mod gland h'perplasia	0 560	0 114	Slight wound infection cleared up quickly *	Died while taking ether at 2d operation

TABLE 2.—EXPERIMENTS IN WHICH

Case No	Sex	Age	Weight	Day, Month, Year of Operation	Part Removed	Weight of Gland Removed	Color	Consistency	Colloid
A 121a	M	Middle	7 3	22, 4, '08	Part of r lobe	4 6	Reddish Yellow	Moderate	Visible
A-121b	M	Middle		28, 4, '08	Part of r lobe	7 6	Reddish yellow	Moderate	Visible
A-121c	M	Middle		9, 5, '06	Part of r lobe	6 4	Reddish, transl	Moderate	Visible
A-121d	M	Middle		21, 5, '08	Part of l lobe	3 6	Reddish, transl	Moderate	Normal
A 121e	M	Middle	8 7	2, 6, '08	Part of l lobe	1 2	Reddish, transl	Moderate	Normal
A-121f	M	Middle		12, 6, '08	Part of l lobe	4 85	Reddish, transl	Moderate	Normal
A 121g	M	Middle		27, 6, '08	Part of l lobe	4 2	Reddish, transl	Moderate	Normal
A 121h	M	Middle		10, 7, '08	Part of l lobe	2 0	Reddish, transl	Moderate	Normal
A-121i	M	Middle	10 9	13, 9, '08	Part of l lobe	0 5	Reddish, transl	Moderate	Reduced
A-121j	M	Middle	12 1	1, 1, '08	Part of l lobe	0 8	Reddish, transl	Moderate	Normal
A-121k	M	Middle	12 0	22, 12, '08	Part of l lobe	0 855	Gray, red, transl	Moderate	Reduced

weeks, one was fed pure iodin by mouth, one ferrous iodid by mouth, and the other was kept as a control We also took three pups raised in the laboratory with histologically normal glands and fed the same amount and kinds of iodin to them In the goitrous pups the loss of weight was very rapid (one-twelfth of body weight in five days) in those fed iodin, and one-fortieth in the pup used as a control On the other hand, the normal pups continued to gain in weight, whether fed iodin or not

This brings up a very important, though well-known, observation, namely, that iodin administered to dogs with hyperplastic thyroids has a physiological action like the desiccated thyroid, i e, it rapidly reduces the body weight, while iodin administered to normal dogs does not Without further data than our anatomic observations we advance the following possible explanation for this phenomenon, which has long been known to students of human goiter In the hyperplastic glands their ability to take up iodin is greatly increased, owing to the greatly increased blood supply and the increased epithelial surfaces of the gland, and the excretory apparatus (whether through the venous or lymph channels) is also greatly increased so that the ability of the gland to give off the iodized protein substance is increased to practically the same extent as is the ability to take iodin from the blood, and until this excretion can be lessened the organism is receiving, in effect, excessive doses of the physiologically active substance As will be recalled from the anatomic

Iodin was Not Given—Continued

Histologic Diagnosis	Iodin per gm , Dried	Iodin per gm , Moist	Complicating Factors in Experiment	Remarks
Colloid, mod gland hyperplasia	0 269	0 059	None	
Colloid, mod gland hyperplasia	0 455	0 099	None	
Colloid, early mod gland h'perplasia	0 692	0 167	None	
Colloid, early gland hyperplasia	1 838	0 520	None	
Colloid, early gland hyperplasia	1 774	0 446	None	
Colloid, early gland hyperplasia	1 427	0 369	None	
Colloid	2 170	0 550	None	
Colloid, early gland hyperplasia	1 091	0 188	None	
Colloid, early gland hyperplasia	1 082	0 196	None	
Colloid	1 925	0 513	None	From 10, 3, '00, to 10, 25, '08, dog was given 15 c c syr ferr iodid by mouth Histology Colloid gland
Colloid, early gland hyperplasia	1 540	0 305	None	Developed tetany 12 27, '08, controlled by CaCl$_2$ and save for tetany, in excellent condition 1, 26, '09

studies, the body proceeds to accomplish this end by gradually inducing obliterating endarteritis accompanied by a lessening of the size of the veins and lymphatic channels from the gland so that these changes are quite evident when the gland has reached the colloid state   (This process has also been recognized and described by v Bruns,[3] by Oelsner[4] and De Ligneris[5]) And, as is well known, the administration of small doses of iodin (not in the form of desiccated thyroid) to normal or colloid glands does not occasion a noteworthy loss of weight   Indeed, clinically, in dogs it induces an increase in weight   Whether these anatomic changes in the vessels accompanying the process of involution (reversion) may be interpreted truthfully as we have here hypothesized is for future experiment and observation to decide   It is, indeed, very suggestive of such a physiologic rôle and may be made use of in clinical experiments with advantage, as we have already done, namely, that of beginning with very small doses of iodin in the hyperplasias and gradually increasing the dosage as the glands approach the quiescent or colloid state We may add also that in exophthalmic goiter we have used the same method and with it have not seen the well-known untoward effect of

3 Bruns   Beitr z klin Chir , 1896, xvi, 521
4 Work done under T Kocher and referred to by him in Arch f klin Chirurg , 1908, lxxxvii, 131
5 De Ligneris   Dissertation, Berne, 1907

either desiccated thyroid or of iodin, as these substances usually have been administered in such cases Thus iodin has a powerful drug action, this action varying with the dosage and with the degree of active hyperplasia of the thyroid and in its administration in all cases of goiter, whether in man or animals, two points should always be borne in the mind, viz   (1) Small doses of iodin accomplish better thyroid effects than larger doses, whether the gland is normal, colloid or hyperplastic, (2) and, while in normal or colloid glands large doses of iodin (not in the form of desiccated thyroid) usually have no untoward thyroid effects, in the case of actively hyperplastic glands the dose must always be inverse to the degree of thyroid hyperplasia

To sum up, then, we have observed

1 The tendency of all active hyperplasias is to revert spontaneously to colloid glands, and this change is hastened or delayed by the presence or absence of iodin The amount of iodin given is of little consequence in normal and colloid glands, but of the greatest significance in the active hyperplasias

2 The ability of the glands to take up iodin does not depend so much on the form, mode or amount of its administration as it does on the degree of active thyroid hyperplasia

3 There is a minimum amount of thyroid tissue below which iodin does not protect against compensatory hyperplasia This limit is roughly the same whether colloid or normal gland

It is probable that desiccated thyroid would further inhibit the hyperplasia, though we have no experiments on this point Such a finding would add to the general belief that there are other activities of the thyroid than that associated with the elaboration of the iodized protein

EXPERIMENTAL CONGENITAL HYPERPLASIA OF THE THYROID IN DOGS

So far as is known to us, Halsted[6] was the first to produce and to recognize the experimental production of congenital thyroid hyperplasia in dogs His observations were made in 1888-9 and included three litters of goitrous pups from three different bitches All these bitches had had part of their thyroids removed (from one to one and a third lobes) prior to impregnation The thyroids were, in two litters, twenty times and, in the other, about twelve times larger than normal pups' thyroids These pups' thyroids showed no differentiation into colloid containing alveoli, as is the case in normal glands, but in general the alveoli were small, undistended tubular structures lined with cubical

6 Johns Hopkins Hosp Rep , 1896, i, 399

epithelium   The whole structure much resembled that of the parathyroid gland

Following this, Edmunds[7] was able to get a similar result in one experiment   Thus far we have seen no records of attempts to produce litters of normal pups from bitches which have previously given birth to goitrous ones, or *vice versa*   It is on this phase of the subject that we wish to record our observations

Dog A-17 —A female dachshund admitted Jan 20, 1907, weight 5 4 kg   Excellent condition   Thyroid lobes not palpable

Jan 22, 1907   Under ether anesthesia the right lobe was removed, weighing 0 7 gm   Excellent recovery   Gross description of the gland removed   Firm, yellowish translucent, colloid visible   Normal vascularity

Histologic Diagnosis —Normal-early glandular hyperplasia   Iodin determination not made   (Specimen lost by accident)

Jan 26, 1907   Wound healed

January 26 to February 7 inclusive   200 mg of iodin were given in the food

February 22, five pups were born, one still-born   The subsequent histories of these five pups are tabulated in Table 3

<div align="center">TABLE 3 —PUPS OF DOG A-17</div>

No of Puppy	Weight Gm	Sex	Age	Day, Month, Year of Operation	Portion of Thyroid Removed	Histologic Diagnosis	Iodin Content	Remarks
A-17α	212	♀	0			Normal fetal thyroid	?	Still-born
A-17β	210	F	3 days	25, 2, '07	Both lobes	Normal fetal thyroid	Trace	Died 18, 2, '07 , unable to nurse
A-17γ	290	?	9 days	3, 3, '07	Left lobe	Normal fetal thyroid	Trace	Died 4, 3 '07
A-17δ	290	F,	9 days	3, 3, '07	Right lobe	Normal fetal thyroid	?	Died 9, 3, '07 , wound infection
A 17ε	?	M	26 days	Autopsy	Both lobes	Normal	?	Died 20, 3, '07 , kerosene poisoning

March 15   The mother had scabies, had lost some weight   Dog was chloroformed to death   Weight at death 5 kg   Left lobe of thyroid was removed at autopsy, weight, 0 65 gm

Gross Description of Left Lobe —Yellowish, translucent   Abundant colloid   Capsule and vessels normal

Histologic Diagnosis —Pure colloid gland (goiter)

Iodin per gm , dry = 4 615 mg   Iodin per gm fresh = 1 093 mg

Dog A-104 —Mongrel fox terrier admitted May 16, 1907   Pregnant   Weight, 7 71 kg   Good condition   The thyroid lobes were not palpable

May 17   Five pups born

May 21   Four pups alive and in good condition

August 27   All pups in good condition

The subsequent histories of these pups are tabulated below

September 7   Bitch impregnated by *non goiterous* fox terrier

September 10   Under ether anesthesia the entire right lobe weighing 1 7 gm , and approximately two thirds of left lobe, weighing 1 45 gm were removed

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7 Lancet, London, 1901, i, 1451

Gross Description of Gland Removed—Yellow, translucent   Consistency firm
Vascularity normal   Capsule thin and delicate   Colloid abundant

Histologic Diagnosis—Pure colloid gland (goiter)

Iodin per gm, dry = 2 739 mg   Iodin per gm, fresh = 0 510 mg

September 16   Dressings removed   Wound healed, had had no evidence of tetany

October 21   Bitch pregnant

TABLE 4—PUPS OF DOG A-104, FIRST LITTER

No of Puppy	Day, Month Year of Operation	Age	Sex	Weight Kg	Portion and Weight of Thyroid Removed	Histologic Diagnosis	Remarks
Pup 1 (T-15)	27, 8, '07	102 days	F	1 6	Left and ½ of right lobe	Normal	Ether anesthesia
Pup 1 (T-15)	4, 1, '08	232 days	F	3 2	Remainder of rt lobe, 0 150 gm	Early gland hyperplasia	Ether anes, died 7, 1, '08, tetany
Pup 2 (T 24)	6, 9, '07	112 days	M	2 8	Lt lobe, 0 350 gm ¼ rt lobe, 0 050	Normal	Ether anesthesia
Pup 2 (T-24)	4, 1, '08	232 days	M	6 4	Part of rt lobe, 0 275 gm	Early gland hyperplasia	Ether anesthesia
Pup 2 (T-24)	20 12, '08 (Autopsy)	279 days	M	7 0	Remainder of rt lobe, 0 150	Mod gland hyperplasia	Distemper—chloroformed
Pup 3 (T-25)	6, 9, '07	112 days	F	1 8	Left lobe, 0 350	Normal	Ether anesthesia
Pup 3 (T 25)	30, 10, '07 (Autopsy)	139 days	F	2 6	Right lobe, 0 355	Mod gland hyperplasia	Killed by another dog
Pup 4 (T-51)	17, 10, '07 (Autopsy)	153 days	M	2 3	Left lobe, 0 700	Normal	Killed by another dog (Kept as control)

November 9   Whelped four pups, the subsequent histories of which are tabulated in Table 5

December 22   Bitch in excellent condition

January 4, 1908   Under ether anesthesia a part of the remaining portion of the left lobe, weighing 2 25 gm, was removed, leaving a piece of thyroid tissue about the size of a small pea   The parathyroid was not seen

TABLE 5—PUPS OF DOG A-104, SECOND LITTER

No of Puppy	Day, Month, Year of Operation	Age	Sex	Weight Gm	Portion and Weight of Thyroid Removed	Histologic Diagnosis	Remarks
Pup 1 (T-73)	14, 11 '07 (Autopsy)	5 days	F	320 0	Both lobes, 0 105 gm	Early gland hyperplasia	Chloroformed (Control)
Pup 2 (T 96)	7, 12, '07 (Autopsy)	28 days	F	960 0	Both lobes, 0 400	Early gland hyperplasia	Killed by another dog
Pup 3 (T-97)	7, 12, '07 (Autopsy)	28 days	F	910 0	Both lobes, 0 305	Early gland hyperplasia	Killed by another dog
Pup 4 (T-2)	24, 12 '07 (Autopsy)	45 days	F	1 110	Both lobes, 0 450	Mod gland hyperplasia	Killed by another dog

Gross Description of Gland Removed—Quite firm and vascular and showed considerable regeneration of the thyroid beyond the old suture line   Color red translucent   Colloid visible

Histologic Diagnosis—Colloid-early glandular hyperplasia   No iodin determination

Jan 7, 1908 Dog died during the night of tetany Autopsy showed evidence of salivation Gastric dilatation Other tissues normal Remaining piece of thyroid weighed 0 230 gm and on histologic examination the ligature was found to have included and caused necrosis of what was probably the only remaining parathyroid

Dog A-112—Female mongrel, admitted Jan 11, 1908 Weight, 5 3 kg Nutrition good Thyroid lobes not enlarged

January 12 Impregnated by a healthy fox terrier

January 15 Under ether anesthesia the whole left and approximately two-thirds of the right lobe were removed The total gland removed weighed 4 15 gms Good recovery

Gross Description of Gland Removed—Dark red in color Moderate consistency Colloid barely visible Lobes appear somewhat enlarged Moderately vascular

Histologic Diagnosis—Moderate glandular hyperplasia

Iodin per gm , dried = 0 332 Iodin per gm , fresh = 0 078

January 18 Jaws slightly swollen, otherwise condition good

January 20 Swelling of jaws had disappeared Appetite good

January 22 Bandage and stitches removed Wound healed The dog received no iodin except what might have been obtained from the food

March 15 Two pups were born, one still-born, mother in good condition The histories of these pups are tabulated in Table 6

TABLE 6—PUPS OF DOG A-112, FIRST LITTER

No of Puppy	Day Month, Year of Operation	Age	Sex	Weight Gm	Portion and Weight of Thyroid Removed	Histologic Diagnosis	Remarks
Pup 1	15, 3, '08 (Autopsy)	0	?	280 0		Fetal type of hyperplasia	Still born
Pup 2	7, 5, '08	52 days	M	1 35	Left lobe, 0 195	Colloid	Fed iodin , ether anesthesia
Pup 2	1, 6, '08	77 days	M	?	½ of right lobe, 0 100	Colloid	Fed iodin , ether anesthesia
Pup 2	7, 12 '08	267 days	M	8 1	Remainder of rt lobe, 0 600	Colloid—marked gland hyperplasia	11, 3, '09, no tetany no myxedema, normal

March 25 Under ether anesthesia approximately one half of the remaining portion of the right lobe was removed Recovery from operation good Piece removed had a normal gross appearance

Histologic Diagnosis—Pure colloid gland (goiter) No iodin determination

March 26, 9 a m Dog in violent tetany Respiration 180 200 per minute Mouth gaping Pulse could not be counted Tongue protruding and of a very bright red color Profuse salivation Dog lay on its side All muscles tense with intermittent general tetanic seizures Was given 5 c c of a 5 per cent calcium chlorid solution in one-half pint of milk by a stomach tube At 4 p m dog was able to walk, though very weak

March 27 Repeated the dose of calcium chlorid with milk Dog still had slight muscular twitchings Respiration 32 Pulse 130

April 1 Calcium chlorid stopped Apparent recovery from tetany Bandage removed, together with stitches Wound healed

April 6 No evidence of tetany, though five days have elapsed since calcium chlorid was stopped

July 3   Dog and pup in good condition   No evidence of scabies, but a prophylactic application of sulphur ointment was given

September 1   Dog in excellent condition

October 1   Sulphur ointment again applied

October 15   Dog pregnant

October 29   Gave birth to five pups

October 30   One pup, weight 115 gm, chloroformed to death   Thyroid lobes histologically normal

November 2   One pup, weight 260 gm, chloroformed to death   Thyroid lobes histologically normal

November 3   Mother in violent tetany, given 50 c c of a 5 per cent solution of calcium chlorid with relief in two hours

November 19   No tetanic symptoms since November 3   5 c c of calcium chlorid solution had been given daily

December 3   Mother and three pups normal   Had weaned the pups

Summarizing these cases, we find that A-17 gave birth to normal pups after one lobe had been removed and iodin administered   The remaining lobe returned to the colloid state, while the first lobe removed was histologically a *normal-early* glandular hyperplasia

In A-104 a litter of normal pups was born shortly after admission, then after nearly four months the dog was again impregnated and one and two-thirds thyroid lobes removed, which histologically were pure colloid glands   In the second litter, the pups' thyroids were slightly enlarged and histologically were in a state of early glandular hyperplasia   The remaining portion of the mother's thyroid had also undergone hyperplasia

In A-112, immediately after impregnation, one and two-thirds lobes were removed, which histologically were in the state of moderate glandular hyperplasia   Of the two pups born, one died at birth and its thyroid was slightly enlarged and histologically showed only cylinders of columnar cells, with no evidence of colloid (fetal type of hyperplasia likened by Halsted to parathyroid tissue)   The mother and pup were given iodin   The pup was reared   The second litter of pups from this bitch (A-112) was normal

These cases, in so far as they show a repetition of Halsted's results, are positive, but they are only suggestive of the inhibiting effect of iodin They do not eliminate the possibility and, indeed, the probability of other factors than iodin as determining the fetal thyroid reaction   We believe that iodin is the greatest single factor, but that the general food and the general hygienic surroundings are also of great importance, since all the cases of congenital goiter examined show general nutritional disturbances, as anemia, bone changes, etc   Such cases in human pathology have usually been included under "fetal rickets"   This fetal thyroid hyperplasia, so far as our observations have extended, seems to

be identical in its anatomic and physiologic characteristics with compensatory hyperplasia following partial removal, and it is likewise identical histologically with the naturally occurring hyperplasias, whether of prenatal or postnatal origin Iodin has similar inhibiting and involuting (reverting) effects in all these forms of hyperplasia

Finally, it seems advisable to add some account of the clinical phenomena accompanying these various anatomic conditions of the thyroid, in order that the rather disconnected anatomic, chemical and general biologic data discussed on the preceding pages may be utilized for clinical inference Again the anatomic grouping must be followed

1 *Normal Glands*—Animals with normal thyroids obviously do not concern us

2 *Colloid Glands*—Animals with colloid glands are, as a rule, adults (unless treated) and present no symptoms referable to the thyroid, save that the glands are usually enlarged, and, for this reason, one may observe mechanical (pressure) effects, although in quadrupeds this is extremely rare All animals (sheep and dogs) whose glands were pure colloid were clinically in excellent health This applies to the colloid glands experimentally produced (by the direct administration of iodin, by food or otherwise), as well as the natural occurring ones

3 *Hyperplasias*—The great majority of all animals (sheep, dogs, cats, horses, hogs and cattle) whose glands were histologically in the state of active hyperplasia showed no symptoms which would distinguish them from normal animals by the ordinary methods of examination This statement is of importance when one recalls that 90 per cent of the dogs and 50 per cent of the sheep and cattle of this locality show hyperplastic changes of a greater or lesser degree On the other hand, there is a degree of hyperplasia which, when present, is always accompanied by clinical manifestations These clinical manifestations are of different degrees, reaching their highest in the true cretins which die shortly after birth, thence shading off gradually to the limit of detectability We have used the term "cretinoid" in order to include the several degrees of severity of the symptoms

All these animals are young (calves, lambs or puppies) In the worst forms the animals die immediately after birth Such subjects show poorly developed hairy coats (thin, coarse), a high degree of anemia and deficient calcification of the bones but with no reduction in the subcutaneous fatty tissue These animals as a rule have much-enlarged thyroids of the glandular-vascular type with prominent lymph glands, thymus and spleen In dogs, the most common types at the laboratory have been the less severely affected subjects—those which

would eventually recover spontaneously   Farmers in Michigan have told us that lambs usually recover if able to suckle   We have found the same to be true of dogs   In these milder cases one notes the following characteristics   The hair is dry, coarse and partially furred   The palpebral fissure is narrow   The eyes are weeping and dull   The heart is hypertrophied   The rate is rapid and the beat forcible   On slight exertion, back pulsation in the neck veins occurs and the thyroid lobes become acutely swollen with blood   This may produce syncopal attacks in which the animal may die   The epiphyses of the bones are enlarged The mucous membranes are very pale, almost blanched So far as we have observed, the appetite is good and the general body bulk is quite or above the average weight   The gait is slow, unsteady, awkward, and mentally they are extremely dull   We have never observed true exophthalmos, although we have imagined in some cases that the eyes were slightly more prominent than in normal pups   These two types illustrate the severest and the moderate degrees   The milder forms down to clinically normal dogs show the same kind of manifestations, the difference being of degree   Excellent and much fuller descriptions of the phenomena in lambs and calves may be obtained from reports by Davis,[8] Seligmann[9] and Campbell [10]

  8 Davis   Vet Jour and Ann Comp Path , 1898, xlvii, 25
  9 Seligmann   Tr Path Soc Lond , 1903 4, lv, 1
 10 Campbell   Tr Med and Phys Soc , Calcutta, 1833 4, vii, 1

OBSERVATIONS ON A CHILD WITH A GASTRIC FISTULA IN RELATION TO RECENT ADVANCES IN THE PHYSIOLOGY OF GASTRIC DIGESTION

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There is no field of medicine in which more activity has been displayed in recent years than in the physiology of digestion Processes that had previously been considered of the utmost simplicity have been shown to be complex and intricate Both secretory and motor functions of the digestive organs have been demonstrated to be remarkably selective and purposive and to be subject to interrelations well beyond our previous conceptions Many of the newer discoveries have been the result of the activity of Pawlow and his followers, and of the methods devised by them, which permit a much more accurate determination of the functions of the digestive organs than had previously been possible Most of the facts that have been determined have been the result of animal experimentation, though some observations have been made on suitable human subjects, they have not as yet been so numerous as to make further contributions to the subject undesirable With this in mind, I made search for an appropriate subject on whom to conduct observations

As the majority of patients on whom gastrostomy is performed suffer from malignant growths, which would be likely, through either their local or their constitutional effects, to cause gross abnormalities of the gastric functions, such patients would obviously be unsuitable for the observations that I desired to conduct I succeeded in finding a suitable subject in the person of a girl, 14 years of age, on whom a gastrostomy had been performed for a complete benign cicatricial stenosis of the esophagus This procedure was carried out eleven years ago by Dr John H Jopson, to whom I wish to express my obligation for bringing the patient to my notice The esophageal obstruction, which resulted from the drinking of lye, is situated at about the level of the bifurcation of the trachea The patient, living in one of the rural districts of Pennsylvania, has grown into vigorous adolescence, feeding herself by means of a small stomach-tube one end of which is inserted into the gastric fistula The other end is tied with a string about the neck so that no portion of the tube is seen except when the patient eats During meals she partakes only of liquid and semisolid foods masticating and swallowing in

the usual way until about three ounces have been taken She then places the upper end of the tube in her mouth and, with a slight voluntary effort at regurgitation, forces the food from the pharynx and esophagus into the mouth and down through the tube into the stomach This process is repeated until the meal is completed The patient apparently enjoys her meals, and possesses the usual childish fondness for sweets and other dainties At my request, she was brought to the University Hospital, where I conducted the observations to be subsequently described

As is almost too well known to warrant repetition, it was the remarkable work of Pawlow[1] that has established, in great part, our present conceptions of the physiology of digestion For the proper comprehension of certain terms and references to be used in this paper it will be well to describe briefly two of the procedures instituted by Pawlow One of these consisted in performing a gastrostomy on a dog and subsequently sectioning the esophagus in the neck, the gastrostomy wound was so treated as to form a permanent fistula, the lower end of the sectioned esophagus was closed and tucked in the wound, while the edges of the upper end, that communicating with the pharynx, were stitched to the skin so as to form a permanent esophageal fistula By means of this combination of operations, communication between the mouth and stomach is completely destroyed Though the dog can chew and swallow food, it passes out of the esophageal fistula instead of into the stomach At the same time any juice secreted in the stomach can be collected, uncontaminated by food or saliva Feeding dogs previously operated on in this way constitutes a "Scheinfutterung" or "false feeding" A second important operation devised by Pawlow consists in establishing practically two gastric cavities The smaller of these, which communicates with the external surface of the body, is so separated from the larger cavity that no substances can pass from the one to the other Its nerve and blood supply are, however, retained so that any influence acting on the main stomach calls forth the same response in the smaller one As the latter communicates with the abdominal surface its secretion can be easily collected It was by means of this procedure that Pawlow investigated the character, rate and amount of the gastric secretion induced by various foods

Probably the most important fact established by Pawlow was that there are two distinct classes of excitants to the flow of gastric juice The first and most important of these consists of the psychic excitants, those which by appealing to one of the senses or higher mental faculties

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1 Die Arbeit der Verdauungsdrusen, Wiesbaden 1898

induce appetite and cause the flow of gastric juice A stimulus that appeals to the psychical processes by means of the senses of taste or smell might be called a psychic stimulus, one inducing appetite by a more indirect route, by appealing to the mental processes by means of the senses of sight, hearing or touch, might be called an indirect, or associated, psychic stimulus In man, even the higher mental processes, memory and imagination, come well within the group of psychic stimuli The second group of excitants of gastric juice consists of the chemical stimuli—those that act only by direct contact with the gastric mucosa Incidentally, Pawlow showed that mechanical stimuli, previously thought to be of profound influence, are totally incapable of inducing gastric secretion

I had hoped to be able to demonstrate on my patient the efficiency of psychic stimuli in inducing gastric secretion, by appealing to the various senses with food and collecting the gastric secretion by means of a catheter introduced into the stomach through the fistula I soon found, however, that this was impossible Although the patient desired to lend herself completely to the experiment, she could not overcome the fact that it was an experiment and distasteful to her This mental attitude was apparently sufficient to inhibit entirely the natural effect of these psychic stimuli The very fact that the stimuli are psychic makes them subject to untold variations, and any other psychic process working at cross-purposes to them is apparently able to nullify them completely

Pawlow encountered numerous instances of this nature in his work on dogs Many of the animals, by reason of their not taking kindly to the experiments, had to be discarded as totally unfit for the proposed observations. Others that ordinarily manifested a vigorous flow of gastric juice, when irritated or angered or otherwise disturbed, failed entirely to manifest the usual secretion

The influence of the emotions on gastric secretion was strikingly seen in some observations of Bickel and Sasaki [2] They had in their laboratory a dog with an esophageal and a gastric fistula, on which they had been making false-feeding observations The animal, which was not of an especially friendly temperament, was found to work himself into a violent frenzy at the sight of a cat that happened to be brought into the laboratory Bickel and Sasaki used this phenomenon to demonstrate the influence of emotional excitement on gastric secretion In a control false-feeding experiment as ordinarily conducted, 66 7 c c of gastric juice were collected in the first twenty minutes after the feeding On a subse-

2 Bickel and Sasaki Deutsch med Wchnschr 1905, xxx, 1829

quent day the dog was allowed to excite himself by watching the cat for a period of five minutes After he had become somewhat calmer, a false feeding was administered under the same conditions as in the control experiment, and in the same period of time but 9 c c of gastric juice were secreted

Quite as profound was the effect of excitement in inhibiting a secretion already instituted The dog was given a false feeding, and in the first five minutes after it 28 5 c c of gastric juice were secreted The cat was then shown to the dog again for five minutes, and the secretion in the subsequent five minutes fell to 3 c c

Bogen,[3] in a series of observations to be subsequently described, on a child 3½ years old, found the same inhibitory effect to result from teasing the child or from inducing pain by means of an electric current

It will serve as of historical interest, as well as a mark of recognition of the powers of observation of a remarkable student of physiology, to state that in 1833 Beaumont[4] observed the same influence in his studies on Alexis St Martin, as shown by the statement, in speaking of the gastric juice "Fear and anger check its secretion "

The importance in clinical medicine of these "negative" psychic processes or emotions, which may work at cross-purposes to the "positive" psychic stimuli to gastric juice, can not be overestimated When we realize their significance, the bearing that worry, anger, grief or excitement may have on the digestive processes becomes at once apparent

Literature is not wanting in instances among human subjects of the effects of psychic stimuli in inducing gastric secretion Even long before the days of Pawlow and his experiments, this influence was observed by Richet[5] in a patient with a gastric fistula, and probably even by Beaumont It is especially as the result of the stimulus given to physiologic research by Pawlow, however, that observations on man have been conducted

Cade and Latarjet[6] had under observation a patient peculiarly adapted to physiologic observations on gastric secretion She was a woman, 20 years of age, who, during childhood, had suffered an accident resulting in a hernia of a small portion of the stomach This hernial sac ruptured spontaneously on the abdominal surface, 2 cm above the umbilicus Later, by the growth of inflammatory tissue, the mucous membrane of the smaller portion became totally separated from the mucous membrane

3 Bogen   Arch f d ges Physiol (Pfluger's), 1907, cxvii, 150
4 Beaumont   Physiology and Experiments, Edition 2, Burlington, 1847, p 81
5 Richet   Jour de l'anat et de physiol, 1878, p 326
6 Cade and Latarjet   Jour de physiol et de path gén, 1905, vii, 221

of the large portion of the stomach As its blood supply and nerve supply were apparently preserved, the condition practically resulted in a human, perfectly functionating Pawlow stomach Aside from some limited observations on the character of the juice secreted in response to various foodstuffs, Cade and Latarjet were able to demonstrate the effect of psychic stimuli by collecting from the small stomach, during a conversation regarding the patient's favorite foods, more than twice the amount of gastric juice secreted during a similar period while the patient was at mental rest It is to be regretted that Cade and Latarjet did not make more exhaustive observations, having such an exceptional opportunity as they did

Bogen conducted observations on a child 3½ years old with a gastric fistula and complete esophageal stenosis He found, first, that the mastication of meat coming in no wise in contact with the gastric mucosa regularly produced a secretion of gastric juice after a latent period of four to five minutes The particular object of Bogen's investigations was to determine the efficiency of associated psychic stimuli in producing a gastric secretion With this end in view, the child was fed with meat at a definite hour each day, and always under the same conditions Coincidently with the feeding, several blasts, always of the same tone, were blown on a small trumpet Finally, after this procedure had been repeated something more than forty times in all, the same blast was blown on the trumpet and no meat was fed Of the ten times that the effect of this associated stimulus was tried, a gastric secretion similar to that obtained when the meat was fed was obtained seven times, in the remaining three times no juice was secreted

Quite as interesting an instance of an accidentally associated psychic stimulus was observed by Bogen on his patient He found that after the feeding of meat had been repeated a number of times, occasionally a sudden vigorous flow of gastric juice presented itself some minutes before the meat was given Watching carefully for the cause of this, Bogen soon found that the stimulus to the flow of juice was the sight of the nurse who brought the child its food conferring with the experimenter preparatory to the expected meal

A much more complete repetition of the Pawlow experiments on an adult was made by Kaznelson[7] on an individual exceptionally adapted to such observations The patient had had a gastrostomy performed when she was 15 years old on account of a complete benign stenosis of the esophagus resulting from the drinking of lye When she was 23 years

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7 Kaznelson Arch f d ges Physiol (Pfluger s), 1907, cxviii, 327

old, an esophagostomy was performed, resulting in a fistula of the upper patulous portion of the esophagus Subsequently a long rubber tube with an upper funnel-shaped end was passed down through the pharynx and upper portion of the esophagus and brought out of the esophageal fistula The lower end of this tube was connected with a tube entering the gastric fistula, so that the patient was able to eat as a normal individual would, the food, after mastication, passing through the tube worn underneath the clothing, instead of through the esophagus The patient thus presented the same conditions as were instituted by Pawlow on animals for false-feeding experiments, and served very well for observations of this nature

In these experiments, the lower end of the tube was withdrawn from the stomach, so that the food, after being masticated and swallowed, passed into a receptacle, instead of into the stomach Kaznelson was able to substantiate on her patient practically all the observations of Pawlow concerning false feeding The mastication of foodstuffs pleasing to the patient consistently produced an abundant flow of gastric juice The latent period was approximately five minutes The simple act of chewing did not call forth gastric juice Kaznelson found, in addition, as did Pawlow on animals, that in man the acidity of the gastric juice is approximately constant, but that the amount of secretion is subject to great variations

Umber[8] had similar positive results in a limited number of observations on false-feeding in his patient with a gastric fistula and malignant stenosis of the esophagus He also had an opportunity of observing the action of an associated psychic stimulus, when his patient suddenly presented a vigorous flow of gastric juice on seeing several pieces of bread and butter unintentionally placed near his bed In his patient, Umber found the latent period to be but three minutes

Hornborg[9] had under observation a 4-year-old boy with a gastric fistula and almost complete occlusion of the esophagus, on whom he conducted experiments similar to those already described He was unable to demonstrate the efficiency of visual stimuli in producing a gastric secretion This circumstance he attributed to negative psychic stimuli, such as I have described, for when the child was shown food, but was not permitted to eat it, he at once became angry and began to cry There was, however, always a vigorous flow when the child was permitted to chew food that he liked, although none of it came into contact with the stomach

8 Umber   Berl klin Wchnschr, 1905, xlii, 56
9 Hornborg   Skand Arch f Physiol, 1903, xv, 209

Bulawinzew[10] conducted a series of observations on hospital attendants with apparently normal digestions Test meals of uniform composition were given them, and the acidity and digestive power of the juice removed by means of a stomach-tube were determined Subsequently the subjects' appetites were excited by appealing to them with stimuli acting on the senses of taste, sight and hearing, after which another meal of the same composition was given, and the acidity and digestive power of the resulting gastric juice again determined Bulawinzew came to the conclusion that psychic stimuli play an important rôle in the production of gastric juice

The observations of Pawlow that have apparently found least substantiation in the experiments on human beings are those concerning the effect that mastication has on gastric secretion Pawlow concluded from his experiments that mastication was powerless to provoke a gastric secretion His experiments consisted in feeding stones to dogs possessing both esophageal and gastric fistulæ The observations on man have been conducted almost exclusively by means of the stomach-tube The investigators who defend the stimulating action of mastication differ as to the particular feature of mastication that exerts the stimulating effect on the gastric secretion Sticker,[11] as the result of his observations on normal subjects and those with digestive disturbances, concludes that the saliva induced by mastication is the potent factor Biernacki[12] attributes to the saliva a subordinate rôle, and looks on other undetermined factors associated with mastication as the important ones in inducing the flow of gastric juice, whereas Riegel,[14] Schule,[14] Riegel and Schreuer [15] and Troller[16] look on the act of mastication itself as the potent factor in inducing the gastric secretion Troller, in his remarkable series of investigations conducted on himself, his associates and his patients, showed conclusively that saliva is not a factor in inducing gastric secretion This he did by permitting patients to chew and insalivate a meal of definite composition This was not swallowed, but spat out into a receptacle Later it was introduced, by means of a stomach-tube, directly into the stomach When subsequently withdrawn, it was found to have produced less secretion than when the same meal was chewed and immediately swallowed

10 Bulawinzew   Russk Vrach, 1903, No 17 Ref Biochem Centralbl 1903 xv, 593
11 Sticker   Samml klin Vortr (Volkmann's), 1887 No 207
12 Biernacki   Ztschr f klin Med , 1892 xxi, 97
13 Riegel   Munchen med Wchnschr , 1899, p 1489
14 Schule   Deutsch Arch f klin Med , 1901, lxxvii, 111
15 Riegel and Schreuer   Ztschn f diätet u physik Therap , 1900, iv 462
16 Troller   Ztschr f klin Med , 1899, xxxviii, 183

From the results of the investigations mentioned, there is no doubt that the mastication of food produces a more vigorous secretion than would result from the introduction of the same food without the intervention of the act of chewing I believe, however, that the observers have somewhat misinterpreted their findings It was found, especially by Troller and by Hornborg, in his observations on his little patient with the gastric fistula, that the chewing of substances of which the patient was fond always produced a greater secretion than did the chewing of an indifferent or a tasteless substance, such as rubber or lemon peel This is a very definite indication that there was something else than the mere chewing that in part, at least, induced the gastric secretion This something was undoubtedly the agreeable taste of the substances, which produced a desire on the part of the patient to complete the act of eating them This desire is nothing more than appetite In other words, it is the psychic stimulus inaugurated through the sense of taste which induces the flow of gastric juice In regard to the flow induced by the chewing of tasteless substances, it is not improbable that in this case the more or less conscious association of the act of chewing with the process of which it is commonly a part, eating, results in a psychic stimulus to gastric juice This association may be thought improbable by reason of an observation of Cohnheim and Soetbeer,[17] who found that the act of sucking in new-born pups induced a flow of gastric juice However, the pups on which these observations had been made were born at night, and, as they were not taken from their mother until the morning, it is probable that, the pups having obtained nourishment by sucking during the night, the act of sucking became associated with nourishment and thus resulted in a psychic stimulus Again, it is not improbable that, just as sucking is an instinct, so is the association of sucking and nourishment inherited

Having encountered the obstacle that I have described in making observations on psychic stimuli with my patient I turned to observations on the chemical stimuli In order to obtain an insight into the functional activity of the stomach as ordinarily computed, an Ewald test-breakfast was administered, the resulting gastric juice showing a total acidity of 62, free hydrochloric acid. 36 The experiments, lasting in all fourteen days, were conducted in the latter part of the afternoons, about five hours after the patient had eaten The stomach was first well washed out with water by means of a small stomach-tube with numerous perforations The stomach was then allowed to become per-

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17 Cohnheim and Soetbeer Ztschr f physiol Chem, 1903, xxxviii, 467

fectly quiescent before any substances were introduced The first observation was on the effect of plain, moderately cool, distilled water One hundred c c were introduced through a tube in the fistula, and at the end of ten minutes 40 c c were recovered, possessing a total acidity of 9, free hydrochloric acid, 8   This experiment was repeated several times, as were almost all the others, with practically the same results in each case, except for slight variations in the amount of fluid recovered From this it is seen that water is a definite chemical stimulus to gastric juice in man, this substantiates one of the facts determined by Pawlow in his work on dogs This effect of water must be kept forcibly in mind in considering the results of the remaining observations, for, as all the substances administered were dissolved in water, the secretion called forth by them must be compared with that induced by a similar quantity of pure water The low degree of acidity obtained in this, as in the remaining observations, is, in all probability, the result of the short time that the fluids were left in the stomach

In order to determine the influence of the administration of hydrochloric acid on the gastric secretion, ten drops of dilute hydrochloric acid dissolved in 100 c c of water were introduced Ten minutes later 66 c c of fluid were recovered, possessing a total acidity of 19, free hydrochloric acid, 17 As the acidity of the solution of ten drops of dilute hydrochloric acid in 100 c c of water is equivalent to 9, it is seen that the acidity of the fluid recovered from the stomach was practically that induced by 100 c c of water plus that of the acid introduced Having repeated this experiment several times with approximately the same result, I believe we are justified in concluding that hydrochloric acid itself, introduced into the stomach, does not induce a secretion of *gastric juice*

The influence of native albumin was determined by introducing 4 grams of egg-albumin dissolved in 100 c c of water At the end of ten minutes 34 c c were recovered, possessing a total acidity of 10, free hydrochloric acid, 7 It is thus observed that the influence of a solution of egg-albumin is practically only that of an equivalent amount of water

Quite a different result attended the introduction of a solution of beef-extract Four grams of one of the commercial beef-juices neutralized and dissolved in 100 c c of water were introduced, and at the end of ten minutes 70 c c were recovered, possessing a total acidity of 34 free hydrochloric acid, 22   When compared with the acidity of the gastric juice induced by an equal quantity of water it is readily appreciated how powerful a chemical stimulus of gastric juice beef-extract are Just what the nature of these substances is has not been det r-

mined   These observations are all in harmony with the results of Paw-low's experiments on the chemical stimulants of gastric secretion in dogs

The observations on the effect of the bitter stomachics (tincture of nux vomica, tincture of gentian comp) were exceptionally interesting Introduced directly into the stomach, they induced no more acid juice than would the same amount of water as that which was introduced with them   When, however, they were given five to ten minutes before a chemical stimulus (solution of beef-extract), they regularly caused a greater secretion than when the latter was given unpreceded by the bitter   Furthermore, a bitter stomachic taken into the mouth caused a greater secretion than if it were introduced directly into the stomach The most vigorous response I obtained was in a series of observations in which the acidity resulting from a solution of neutralized beef-extract was   Total, 33 , free hydrochloric acid, 23   When preceded by 4 grams of tincture of gentian comp , introduced directly into the stomach ten minutes before, the secretion rose to, total acidity, 38 , free hydrochloric acid, 26   When the same quantity of gentian was taken into the mouth and kept in the pharynx and upper pouch-like portion of the esophagus for ten minutes preceding the introduction of the beef-extract, the acid-ity rose to, total, 53 , free hydrochloric acid, 40   I subsequently attempted to have the patient take the bitter into the mouth and then introduce it into the stomach to determine whether the combined action was more powerful than either one individually, but the bitter taste was so objec-tionable that I could not persuade her to do so   From these observa-tions, though not carried to the conclusion that I would desire it seems evident that bitter stomachics, principally by reason of their action dis-played in the mouth and pharynx, have a stimulating effect on the secre-tion of gastric juice   Their action locally in the stomach, though not so profound as the former, is, nevertheless, definite

Several observers have come to the same conclusion in regard to the stimulating effect of bitter stomachics   Borrisow[8] found that when he preceded a false feeding in dogs by the application of a bitter stomachic to the mouth and pharynx, over a period of a few minutes, the resulting gastric secretion was more than 30 per cent greater than occurred when the false feeding was not preceded by the application of the bitter Hoppe,[19] and also Straschesko,[20] found that a bitter tonic, of itself, in-duced no secretion , but that when it preceded a false feeding it always

18 Borrisow   Arch f exper Path u Pharmakol , 1904, li, 363
19 Hoppe   Berl klin Wchnschr , 1905, xxxii, 1038
20 Straschesko   Russk Vrach, 1905, quoted by Hoppe, Berl klin Wchnschr , 1905, xxxii, 1038

resulted in an increased secretion of gastric juice Kaznelson, in her observations on a human subject, came to the same conclusion

Pawlow, and subsequently several other observers, found that alkalies inhibited gastric secretion It was impossible, in my patient, to make any reliable observations of the effect of alkalies on secretion. It was of interest, however, to determine their action in regard to gastric motility A solution of 2 grams of sodium bicarbonate in 100 c c of water was introduced, and at the end of ten minutes 9 c c of a solution possessing neither free nor total acid was recovered The bearing that this observation has on gastric motility will be discussed later

Several other observations, though not of so much significance as those already mentioned, are clinically or physiologically of some interest Tea, generally employed as an element of the test breakfast, was found to have the same effect in inducing secretion as a similar quantity of water Various commercial preparations of pepsin were introduced, but were found to have no more effect than that of the amount of water introduced with them Finally, a nutrient enema was administered while the stomach was empty, and within the first fifteen minutes after its administration 12 c c of rather viscid gastric secretion was obtained, possessing a total acidity of 15 and free hydrochloric acid of 11   A similar result was obtained by Umber with his patient

In addition to the bearing that the foregoing observations have on gastric secretion, several of them permit of interesting deductions on some of the phases of gastric motility We are indebted, to a great extent, to Cannon[2] for our present conception of the action of the pyloric sphincter and the control that it has on the emptying of the stomach Cannon's experiments have shown that when food is introduced into the stomach the pylorus closes and remains closed until the necessary conditions are instituted for its periodic opening These conditions are established by the reaction of the contents on the gastric and duodenal sides of the pylorus An acid reaction on the gastric side and an alkaline reaction on the duodenal side tend to open the pylorus, whereas an acid reaction on the duodenal side and an alkaline reaction on the gastric side tend to keep the pylorus closed It is readily appreciated how nicely this mechanism harmonizes with the secretory functions of the stomach and duodenum When food is taken into the stomach it is retained there until a portion is sufficiently acidified and, we can assume also peptonized to be ready for intestinal digestion, when the pylorus opens and lets this portion through into the duodenum Here, by reason of its acid reaction, this acidified portion tends to the closure of the

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21 Cannon Am Jour Physiol, 1907, xx, 283

pylorus until the alkaline pancreatic juice and bile sufficiently change its reaction to induce the pylorus to open again   By means of this mechanism the food is held in the stomach until gastric digestion is sufficiently advanced, and the duodenum is protected from the danger of having an overwhelming amount of acid chyme poured into it at one time   This mechanism apparently sufficiently explains the operations of the pyloric sphincter under normal conditions, and when the reactions on the two sides of the pylorus are different, that is, either acid on the duodenal side and alkaline on the gastric side, or alkaline on the duodenal side and acid on the gastric side

It does not, however, give an insight into the relations that are maintained in those conditions in which the same reaction, either acid or alkaline, is present on both sides of the pylorus   Under these circumstances the behavior of the pylorus must depend upon whether the predominating influence rests in the stomach or in the duodenum   It is on this phase of the subject that the observations described above throw some light

It will be noted, on comparing the secretion resulting from the introduction of the acid solutions and of the alkaline solutions that much larger amounts were returned from the acid than from the alkaline solutions   After a period of ten minutes but 9 c c were recovered from the stomach after the introduction of an alkaline solution, whereas, 66 c c were recovered after the introduction of an equal amount of an acid solution   These observations were repeated a number of times, with variations of but a few cubic centimeters from the figures given   If the reaction on the gastric side of the pylorus exerted the predominating influence, it would be expected that the acid solution would tend to more frequent or more prolonged opening of the pylorus and, consequently, to the passage of a proportionately greater amount of fluid into the duodenum than occurs after the introduction of the alkaline solution, which would, according to the same hypothesis, tend to keep the pylorus closed I believe the phenomena that I have observed to be best explained on the following hypothesis

When an acid solution is in the stomach the phenomena of pyloric discharge observe the mechanism described by Cannon   By reason of the acidity on the gastric side the pylorus opens and a portion of the acid contents is shot into the duodenum   Here, by reason of the same reaction, it closes the pylorus, though acid may still be present on the gastric side   This, then, is an indication of the greater influence of the reaction on the duodenal side, when the reaction on both sides of the pylorus is acid, and the relatively slow discharge of the stomach contents is due

to the time consumed in neutralizing the acidity in the duodenum. When however, the reaction on the gastric side of the pylorus is alkaline, as in the introduction of a solution of sodium bicarbonate, the original opening of the pylorus can, obviously, not depend on acidity in the pyloric antrum. A portion of the gastric contents must be discharged into the pylorus in spite of the alkaline reaction on the gastric side. As soon as it arrives in the duodenum its already alkaline reaction combines with the alkaline reaction of the duodenal secretion and tends to either the frequent or the prolonged opening of the pylorus, and as a result, a much larger amount of fluid passes into the duodenum in a given period of time than when a more acid solution is present in the stomach. From this we draw the conclusion that if the reaction on both sides of the pylorus is alkaline the reaction on the duodenal side is again the predominating one.

If our reasoning thus far is correct (and I believe that it must be to explain the phenomena observed) we may go even farther. If the reaction in the duodenum is the predominating one when the same chemical reaction is present on both sides of the pylorus, and if (as seems beyond doubt, from the work of Cannon and other investigators) it is the predominating one when the reaction is alkaline on one side and acid on the other, then the problem resolves itself into the reaction prevailing in the duodenum being the controlling element in the pyloric mechanism and the reaction on the gastric side being of secondary importance. This hypothesis finds some substantiation in the recent experiments of Foster and Lambert,[22] who were unable to hasten evacuation of the stomach by increasing the gastric acidity without altering the chemical reaction in the duodenum. Cannon, however, was able to delay evacuation by decreasing the acidity of solid food introduced into the stomach.

As the observations from which the foregoing conclusions have been drawn were made entirely with the use of liquids it may be that the behavior of the pylorus toward liquids is different from its behavior toward solids. Cannon believes this to be the case and presents as a possible explanation the view that liquids do not excite the pyloric tonus that is manifested when solid food is ingested. It appears from the evidence presented above, however, that liquids of acid reaction and those inducing a secretion of considerable amounts of hydrochloric acid do excite pyloric tonus. Moreover, several clinical facts suggest the same behavior toward solid food, in diseased conditions, as have been described above for liquids. One of these is the relative frequency with which cases

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22 Foster and Lambert. Jour. Exper. Med., 1908, x, 820.

of simple anacidity or achylia gastrica, without malignancy, are associated with rapid emptying of the stomach and persistent diarrhea only to be controlled by correcting the gastric secretory deficiency, and not less frequently are observed cases of hyperacidity with delayed emptying of the stomach, improving when the hyperacidity is reduced

With the hope of observing the motor behavior of the stomach toward liquids, especially water, a cystoscope was kindly introduced by Dr B A Thomas through the fistulous opening in my patient when the stomach was filled with water, but nothing more than the intermittent opening of the pylorus could be observed It has recently been asserted by Cohnheim[23] and others that when water is swallowed, instead of entering the fundus, as solids do, it enters a small gutter formed by a horse-shoe-shaped band of muscle along the lesser curvature of the stomach, running from the cardia to the pylorus He maintains that, even when the stomach contains food-masses, water does not come into contact with these, but, running through this gutter-like channel, passes immediately into the duodenum This view is scarcely in harmony with the observations of the stimulating action of water on the flow of gastric juice, and no such formation as has been described could be seen in my patient by means of a cystoscope It must be granted, however, that in this instance water did not enter at the cardia, as in normal individuals Cohnheim's claim is somewhat substantiated by the anatomic investigations of Kaufmann,[24] who describes this horseshoe-shaped bundle of muscle running from the cardia to the pylorus

This leads us to consider for a moment the motor functions of the stomach and the arrangement of foodstuffs when taken into it Though Grutzner[25] has shown the fallacy of the old idea of a general admixture of all food taken into the stomach, his views have, as yet, received little general recognition Among the more recent workers to substantiate Grutzner's claim is Prym[26] The investigations of these two experimenters were carried on by feeding animals with foods of different consistency or different color, killing them at various periods of gastric digestion, and immediately freezing or coagulating the stomach and its contents According to their observations, in the fundus, the portion in which active acidification and peptonization occurs, there is a distinct layer-like arrangement of the food In general, the first food taken assumes the outermost position, that is, next to the mucous membrane

23 Cohnheim   Munchen med Wchnschr, 1907, liv, 2581
24 Kaufmann   Ztschr f Heilk, 1907, xxviii, 203
25 Grutzner   Arch f d ges Physiol (Pfluger's), 1905, cvi, 463
26 Prym   Munchen med Wchnschr, 1908, lv, 57

That subsequently taken lies nearer the center of the cavity. This holds true if all the food taken is of the same consistency, or if that first taken is the more fluid. If the more solid elements are taken first and subsequently the more liquid, the wave-like motion of the fundal portion of the stomach-wall forces the solid particles more and more toward the center of the cavity so that eventually the more fluid portions of the contents assume the peripheral position. Only those portions in contact with the mucous surface of the stomach become acidified and peptonized. Those portions farthest from the mucous membrane remain totally un-acidified for considerable periods of time.

In considering the motility of the stomach, the fundal and pyloric portions must be considered as quite distinct. From the time that the food enters the stomach, there is a gentle wave-like motion running from the cardia toward the pylorus. This extends to about two-thirds of the distance from the cardia to the pylorus, where the antrum pylori commences. This wave-like motion gradually sweeps the peripheral portion of the contents of the fundus which have been acidified and liquefied into the antrum pylori. At the beginning of the antrum pylori, the circular band of muscle becomes much thicker and, by its forcible contraction, practically divides the stomach cavity into two distinct chambers, the antrum pylori and the fundus. The antrum pylori, consisting of the pyloric third of the stomach, exhibits, instead of this almost continuous wave-like action of the fundal portion, an intermittent, extremely forcible contraction which forces its acidified contents into the duodenum when the pylorus relaxes.

It is interesting in connection with these newer observations to note the following remarks which were written by Wilson Philip[27] almost a century ago and have apparently entirely escaped the attention of recent writers.

When the foregoing experiment is considered it will appear, either that the food last received into the stomach is never mixed with that already there, and which has more or less undergone the action of the gastric fluid, or if they be mixed together, that the stomach has the power of again separating them, retaining the one and propelling the other into the intestine. These facts induced me to make some experiments on a large scale, for the purpose of ascertaining with great accuracy the process which takes place in the stomach, without which it is impossible to understand the nature of the symptoms which arise from its defects.

With this view I examined the stomachs of about a hundred and thirty rabbits immediately after they had been killed in the usual way, which is by a blow on the back part of the head, at various periods of digestion. The following were the results.

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27 Philip, A. W. Wilson. A treatise on indigestion, Edition 2, Philadelphia, 1822, p. 31

The first thing that strikes the eye on examining the stomachs of rabbits which have lately eaten is, that the new is never mixed with the old food The former is always found in the center, surrounded on all sides by the old food, except that on the upper part between the new food and the smaller curvature of the stomach there is sometimes little or no food   If, as we ascertained by more than twenty trials, the old and the new food be of different kinds, and the animal killed before a great length of time has elapsed after taking the latter, the line of separation is perfectly evident, so that the old may be removed without disturbing the new food   To ascertain this point we fed rabbits on oats, and after making them fast for sixteen or seventeen hours, allowed them to eat as much cabbage as they choose, and killed them at different periods, from one to eight hours, after they had eaten it

On opening the stomachs of rabbits three or four weeks old, who both sucked and ate green food, we always found the curdled milk unmixed with the green food   Before the stomach was opened we could, from its transparency, see where the green food and where the milk lay

If the old and the new food be of the same kind, and the animal be allowed to live for a considerable time after taking the latter, the gastric fluid passing from the old to the new food and changing, as it pervades it, renders the line of separation indistinct   So that on a cursory view we should suppose the old and the new food mixed together, but toward the small curvature of the stomach and still more toward the center of the new food, we find it, unless it has been very long in the stomach, undisturbed and comparatively fresh   All around, the nearer the food lies to the surface of the stomach the more it is digested   This is true even with regard to the food in the small curvature, compared with that nearer the center, and the food which touches the surface of the stomach is more digested than any other found in the same part of the stomach, but, unless the animal has not eaten for a great length of time, the food in contact with the surface of the stomach is in very different stages of digestion in different parts of this organ   It is least digested in the small curvature, more in the large end, and still more in the middle of the great curvature

The foregoing observations apply to the cardiac portion of the stomach, the food in the pyloric portion is always found in a state very different from that just described   It is more equally digested, the central parts differing less from those which lie near the surface of the stomach   It is evident, however, that all the change effected in the stomach is not completed when the food enters this portion of it, because we find it more digested the nearer it approaches the pylorus, where, being ready to pass into the intestine, it has undergone all that part of digestion which is performed in the stomach

It appears that in proportion as the food is digested it is moved along the great curvature, where the change in it is rendered more perfect, to the pyloric portion   Thus the layer of food lying next the surface of the stomach is first digested, and in proportion as this undergoes the proper change, is moved on by the muscular action of the stomach, that next in turn succeeds to undergo the same change   As the gastric fluid, to a certain extent, pervades the contents of the stomach, though apparently in no other way than by simple juxtaposition for the arrangements of the food, above described, we never found disturbed, the change in each part, which in its turn comes in contact with the stomach, is far advanced before it is in actual contact with it, and consequently is soon after this in a proper state to be moved on toward the pyloric end

Thus a continual motion is going on, that part of the food which lies next to the surface of the stomach passing toward the pylorus, and the more central parts approaching the surface, whether food is ever so digested in the small curvature as to be sent to the pyloric portion without having traversed the large curvature, I have not been able to ascertain   When rabbits have fasted sixteen or eighteen

hours the whole food found in the cardiac portion which is in small quantity compared to what is found in it after a fast of short duration seems to be all nearly in the same stage with that next the surface of the large curvature, the gastric fluid having pervaded and acted on the whole, and is consequently, as far as we can judge prepared to be sent to the pyloric end

Although the food is in the most digested state in the pyloric end it appears from the fact just mentioned, and several other circumstances, that the change is chiefly effected in the great end of the stomach

From all that has been said it appears that the process which the food undergoes in the stomach is that of being formed into a mass in appearance nearly homogeneous that the process takes place only on or near the surface of the stomach and that in proportion as the food there situated undergoes the necessary change it is by muscular power of the stomach moved onward toward the pylorus, making room for that which next succeeds until the whole contents of the stomach have undergone this process the digested contents being regularly discharged into the duodenum, as they arrive at the pylorus, till most, and in some animals all the contents of the stomach are thus removed into that intestine from which, after they have for some time been detained there and mixed with bile and pancreatic fluid they are continually passing into the adjoining parts of the canal

If there are varying degrees of admixture of food and gastric juice in the different layers of the stomach-contents, and if the pyloric portion of the stomach-cavity contains only the well acidified and peptonized portions of the ingested material, it would be expected that the different portions of the stomach-contents would reveal varying degrees of acidity and peptic activity Investigations have proved this to be correct Sick[28] by means of a stomach-tube the lower end of which could be opened at will, found that the acidity of the fundal and pyloric portions of the gastric contents differed at different periods of gastric digestion Shortly after food is taken, the acidity of the fundal contents is the greater, later in the process of digestion the acidity of the pyloric region exceeds that of the fundus

More recently Landerer[29] has shown similar conditions to exist in the peptic activity of the fundal and pyloric contents At first, that of the fundus is the greater, later, that of the pylorus becomes the greater

Taussig and Rush[30] have studied the bearing that this separation of the fundal and pyloric portions of the stomach has on the interpretation of a test meal They found that the amount of gastric contents obtained when the patient was in the sitting posture was usually much less than that obtained when the patient was first in a sitting position, then lying on the back, and finally lying on the right side In the two latter postures they obtained from 17 to 65 c c more than could be obtained in the sitting posture Finally, by introducing a known quan-

28 Sick   Deutsch Arch f klin Med, lxxxviii, 169
29 Landerer   Deutsch Arch f klin Med, 1908, xciii, 563
30 Taussig and Rush   Boston Med and Surg Jour, 1908, clviii, 79

tity of water, they recovered from 11 to 64 c c of contents that could not be recovered by any of the former procedures In studying the acidity of the first two portions removed from a series of 28 cases after an Ewald test breakfast Taussig and Rush found them to be approximately equal in eleven instances The first portion was decidedly more acid than the second in fourteen instances, the reverse being true in three instances In one case a difference of more than 50 in the total acidity of the two portions was observed Taussig and Rush believe that their observations destroy, to a great extent, the value of the results obtained by the administration of a test meal I think that they take too unfavorable a view of the subject In the vast majority of subjects, by manipulating the stomach-tube, a certain amount of nausea can be produced, and, as this induces a tendency to vomit the reversed peristalsis incident to this act will cause a fairly uniform admixture of all portions of the stomach-contents

It has long been known that in various circumstances the regurgitation of bile and pancreatic juice into the stomach occurs Beaumont noticed that the introduction of oil into the stomach of his patient caused the appearance of this phenomenon It is only recently, however, that the constancy of this regurgitation under definite conditions has been well established Boldyreff[31] observed that in dogs the introduction of oil or of any strongly acid solution regularly induced a regurgitation of bile, pancreatic juice, and succus entericus from the duodenum into the stomach, and that the same phenomenon occurred occasionally when the stomach had been empty of food for a considerable period of time and no oil or acid was introduced

Investigating the frequency of this phenomenon in man, Volhard[32] was able to demonstrate the presence of trypsin in the stomach after an oil test meal in 86 per cent of the cases studied Faubel,[33] in a similar investigation, obtained a positive result in but 70 6 per cent of his cases He thinks it probable that this low percentage can be accounted for by a technical inaccuracy in his trypsin estimations Lewinski[34] had positive results in practically the same percentage of cases as did Faubel When, however, he neutralized the gastric acidity before the introduction of the oil trypsin was found in all the cases More recently, Molnar[35] observed regurgitation of the duodenal secretions after the introduction of oil into the stomach in 48 out of 50 cases The two patients in

31 Boldyreff   Arch f d ges Physiol (Pfluger's), 1907, cxxi. 13
32 Volhard   Munchen med Wchnschr , 1907, liv, 403
33 Faubel   Beitr z chem Physiol u Path (Hofmeister's), 1907, x, 35
34 Lewinski   Deutsch med Wchnschr , 1908, xxxiv, 1582
35 Molnar   Ztschr f klin Med , 1909, lxvii, 189

whom it did not occur suffered with carcinoma of the pylorus. If the constancy of the phenomenon is substantiated it may prove to be of no little value in the diagnosis of obstructions of the pancreatic and common bile ducts, and it is not impossible that future elaborations may make it of assistance in the diagnosis of functional derangements of the pancreas and liver.

SUMMARY

Summarizing the results of the experiments and observations that have appeared in the literature and those that I have conducted we may say that the importance of psychic stimuli in the production of gastric juice as determined by Pawlow and others in animals applies equally well to man. These psychic stimuli may be conveniently classified as positive and negative. Positive psychic stimuli are those which induce a flow of gastric juice. Negative psychic stimuli (if so paradoxical an expression be permissible) are those which inhibit or annul a gastric secretion. Psychic stimuli both positive and negative may originate in the higher mental processes as memory and imagination or, as is more usual, they may come from without and influence gastric secretion by appealing to any one of the five senses. Those stimuli which influence gastric secretion by appealing to the senses of taste or smell may be called direct psychic stimuli, those that act through the other senses or originate in higher mental processes may be called indirect or associated psychic stimuli. This dependence of gastric secretion on psychical processes and stimuli permits the formulation of the statement that appetite is the emotional expression of the group of phenomena of which the secretion of gastric juice is the physical expression.

The mechanical act of chewing seems to be powerless to induce a secretion of gastric juice. If the act of chewing becomes mentally associated with the process of eating agreeable food it probably is capable of inducing a flow of gastric juice.

The human stomach appears to behave in the same way toward chemical stimuli as does the dog's stomach. Water is a definite though not a powerful stimulus to gastric secretion. Hydrochloric acid is not a stimulus to gastric secretion. Egg-albumin does not induce the secretion of any more gastric juice than does an equal amount of water. The same is true of tea and commercial preparations of pepsin. Beef extracts are powerful stimuli to the secretion of gastric juice.

Bitter stomachics, though of themselves incapable of inducing a secretion of gastric juice, when administered previous to a substance which does induce a secretion of gastric juice, are capable of increasing this secretion. They may, in other words, be looked on as sensitizers of

gastric secretion   This sensitizing action is manifested when the stomache is introduced directly into the stomach or when it merely remains for a time in the mouth and pharynx   Its action seems to be more powerful in the latter case than in the former

It appears probable from the observations I have made on the effect of the introduction of acid and alkaline solutions into the stomach that the predominating influence in the control of the periodic opening of the pylorus is excited by the chemical reaction of the contents on the duodenal side of the pylorus   Though the chemical reaction prevailing on the gastric side of the pylorus is of importance in the pyloric mechanism, it is distinctly subordinate to that on the duodenal side   This hypothesis explains the slow discharge of gastric contents of high acidity and the more rapid discharge of gastric contents of low acidity

As observed by Wilson Philip almost a century ago, and as more recently determined by Grutzner, Prym and others, the food in the stomach of the lower animals undergoes a layer-like arrangement   the liquid food and the solid food first introduced take a peripheral position, next to the mucosa, while that introduced later takes a more central position   As the portion next to the mucosa is peptonized and liquefied it is swept by the wave-like motion of the fundal wall into the antrum pylori preparatory to being ejected into the duodenum, when the next layer in the fundus comes into contact with the mucosa to be subjected to the same process   Though it has been impossible to repeat these observations in man, the same phenomena in all probability occur in the human stomach

The regurgitation of bile and pancreatic juice from the duodenum into the stomach after the introduction of oil into the empty stomach seems to occur with great constancy in normal individuals   If future observations show this to be correct the phenomenon may prove to be of great clinical assistance in the diagnosis of affections of the pancreas and liver and of their excretory ducts in particular

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THE ABSENCE OF ADRENALIN IN MALIGNANT RENAL HYPERNEPHROMAS[*]

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In view of the rather extensive discussion as to the origin of the so-called malignant hypernephromas of the kidney, it is strange that practically no attempt seems to have been made to determine whether adrenalin-like substances are present in these tumors. Investigation of most of the literature on hypernephromas fail to show any instances in which the presence of blood-pressure raising substance has been sought, although a few authors call attention to the existence of a marked arterio sclerosis in patients dying of hypernephroma and suggest that the arteriosclerosis may be the result of a flooding of the blood with excessive quantities of adrenalin. A case of this kind is described by F. J. Hall[1] in which a patient aged 56 with a hypernephroma of long duration showed a most extensive calcareous infiltration of the arteries throughout the body. On the other hand von Hansemann[2] reports that he could find no evidence of arteriosclerosis in fatal case investigated by him. The only experimental evidence brought forward to show the presence of adrenalin in hypernephroma is the observation by Federoff[3], that the extract of a hypernephroma caused dilatation of the pupil of the isolated eye of the frog, which is a most delicate test for adrenalin. He did not try the effect of this extract on blood-pressure or make any other tests for adrenalin.

On the other hand, our own observations on two specimens of malignant renal hypernephroma, one of which was kindly furnished by Dr. F. R. Zeit, the other by Dr. J. W. Jobling, gave entirely negative results.

FIRST TUMOR

Preparation of the Extract—The tumor was carefully removed from the connective tissue capsule and other non-tumor tissue thoroughly crushed, mixed with three times its wet weight of distilled water and allowed to extract with repeated agitations for six hours. This extract

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[*] From the Laboratories of Physiology and Pathology of the University of Chicago

1 Hall, F. J. Hypernephroma. THE ARCHIVES INT. MED., 1908, ii, 355

2 Von Hansemann. Ztschr. f. Krebsforsch., 1908, iv, 570

3 Federoff. Folia Urol., 1908, ii, 551

was very slightly acidulated and boiled to remove the protein The coagulable protein was then filtered off, sufficient sodium chlorid added to make the filtrate of 0 9 per cent strength, and the filtrate rendered sterile by boiling As a control for this method of procedure the fresh adrenal glands of a normal dog were extracted in exactly the same way Before using this latter extract it was diluted to one in ten, so that as far as the amount of the substance extracted is concerned the tumor extract should be two and one-half times as strong per equal volume

These extracts were tested for adrenalin in three ways, as follows

1 Effect on the Blood-Pressure of Two Normal Dogs.—Tracing 1 is the result obtained on the first dog tried The animal was in good condition and was kept under light but constant anesthesia The different solutions were injected intravenously as indicated in the tracing It is to be noted that in every case the intravenous injection of the tumor extract produced a very slight rise, followed by a marked fall in the blood-pressure This preliminary rise is no more than is caused by an equal amount of physiologic salt solution, as is shown by the tracing The fall in the blood-pressure is similar to that produced by extracts of all organs except the adrenal and the hypophysis For a control of this experiment, injections of different-sized doses of adrenalin chlorid were used It will be noted that the injection of 1 c c of a 1 to 30,000 solution produced a striking rise in the blood-pressure, when compared with the slight initial rise after the injection of the tumor extract or of the salt solution

Tracing 2 was taken on another dog, using the same tumor extract as in the first dog, but instead of using adrenalin chlorid as a control the adrenal gland extract referred to above was used In this case 50 c c of the tumor extract were injected at one time This is noted at 9 (Tracing 2) This caused a marked fall in blood-pressure without any initial rise As a control for this experiment 0 5 c c of the extract of the adrenal gland were injected (11, Tracing 2) This produced a marked rise in the blood-pressure, typical of adrenalin It can be seen from the size of the dose of the tumor extract and of adrenal extract that the dose of the former was relatively two hundred and fifty times as large as the latter

2 The Frog's Eye Test.—This test was described by Ehrmann,[4] who appears to be the first to apply and describe this test It depends on the property of adrenalin to stimulate the plain musculature that is innervated by the sympathetic nervous system The test consists of taking the enucleated eye of the frog and placing it in the solution to be tested In

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4 Ehrmann Arch f exper Path u Pharm, 1905, liii, 97
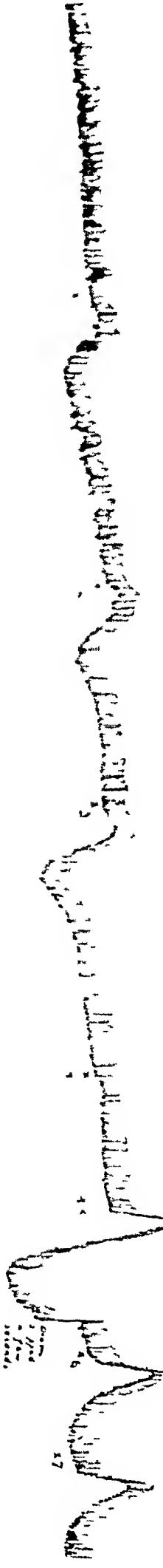
Tracing 1 —March 11, 1900 Weight of dog 12.5 kilo. Blood pressure from the carotid artery. Intravenous injections into the femoral vein. Time tracing in seconds. Index to tracing. 1 Injection of 5 cc tumor extract 2 Injection of 10 cc tumor extract 3 Injection of 15 cc tumor extract 4 Injection of 15 cc 00 per cent NaCl sol 5 Injection of 5 cc 1/30000 adrenalin chlor 6 Injection of 2 cc 1/30000 adrenalin chlor 7 Injection of 1 cc 1/30000 adrenalin chlor
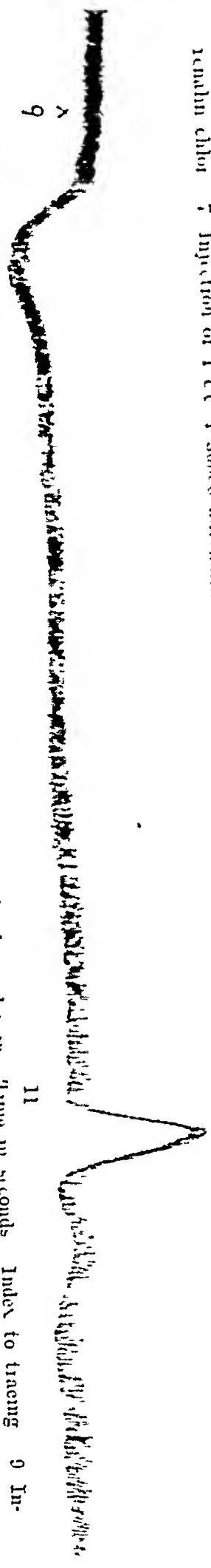
Tracing 2 —Blood pressure from carotid artery. Intravenous injection into the femoral vein. Time in seconds. Index to tracing 9 Injection of 50 cc of tumor extract 11 Injection of 0.5 cc of adrenal gland extract
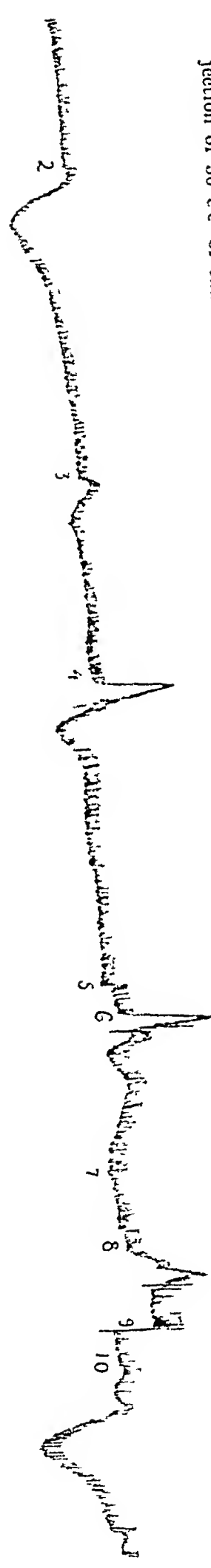
Tracing 3 —Blood pressure from carotid artery. Intravenous injection into the femoral vein. Index to tracing a—b, one minute time 2 Injection of 30 cc tumor extract 3 Injection of 30 cc 0.9 per cent NaCl sol 4 Injection of 3 cc adrenal gland ext 5 Drum stopped 6 Injection of 3 cc adrenal gland ext 7 Drum stopped 8 Injection of 5 cc 1/50000 adren chlor sol 9 Drum stopped 10 Slow injection of 50 cc tumor extract

the presence of very small quantities of adrenalin the eye of the frog shows marked dilatation. Ehrmann asserts that by this test adrenalin can be detected in a dilution as high as 1/10,000,000. Several tests were made of the tumor extract according to this method. A record of one of these tests is as follows:

Substance Tested	Dilatation of Eye	Time Required for Effect
Adren Cl 1/50000	Complete	10 minutes
Adren Cl 1/100000	Complete	18 minutes
Adren Cl 1/500000	Complete	60 minutes
NaCl (0 9%)	No dilatation	Up to four hours
Tumor extract	No dilatation	Up to four hours
Adrenal gland extract	Complete	30 minutes

It will be noted that this test was entirely negative, in fact, the size of the pupils placed in the tumor extract actually decreased.

3 The Colorimetric Test.—A rather delicate chemical test for the presence of adrenalin is the colorimetric one first described and applied by Comessatti.[5] This test is made by adding to the solutions to be tested equal amounts of a solution of mercuric chlorid. In the presence of adrenalin the solution turns pink, the depth of the hue depending on the amount of adrenalin. This test does not appear to be as delicate, however, as that with the frog's eye, for we could not get a positive reaction in a dilution of 1/500,000 of adrenalin chlorid, a strength of which is easily detected by the eye test. By this test the tumor extract gave entirely negative results, while the adrenal gland extract gave a strongly positive reaction.

SECOND TUMOR

This tumor was received fresh and was treated in exactly the same way as the other tumor, with this one exception, namely, that it was extracted for twelve hours, as against six for the former. For control of this extract another adrenal gland extract was prepared in exactly the same way as the tumor extract. This gland extract was also diluted to 1 in 10 as in the former case.

Tracing 3 gives the results of the injection of these extracts on the blood-pressure in a dog. In this case on the injection of 30 c c of the tumor extract there was a slight initial rise in the blood-pressure followed by a marked fall. Here again the initial rise caused by the tumor extract is no more than that produced by the same amount of salt solution. An injection of 3 c c of the adrenal gland extract produced a very marked rise in the blood-pressure. This is shown at 4 and 6 in Tracing

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5 Comessatti Munchen med Wchnschr., 1908, lv, 1926

3 This tracing also shows the effect of a dose of 5 cc of 1 30,000 adrenalin chlorid and of 50 cc of the tumor extract (8 and 10)

Frankel[6] has recently described the extreme delicacy of the test for adrenalin with the uterus of the rabbit He asserts that when immersed in solutions containing as little adrenalin as 1 part in 10 to 20,000,000 the uterus will go into tetanus This tumor extract was tested in this way, but instead of showing the presence of adrenalin by going into the typical tetanus the uterus quickly lost completely its irritability.

The tests with the frog's eye and with the mercuric chlorid were entirely negative in repeated attempts

GENERAL CONSIDERATIONS

The absence of the blood-pressure raising principle of the adrenal from these tumors does not however, indicate that the tumors derived from adrenal rests in the kidney This raising principle of the adrenal is the product of the medullary portion of the gland, which is quite distinct from the cortex functionally, embryologically, and so forth[7] Hypernephromas reproduce the cortical portion of the adrenal, which is derived from the same embryonal anlage as the adrenal, and the cortex which structurally resembles quite closely the corpus luteum, and that functionally seem to have nothing to do with blood pressure, but rather to be related to the generative functions[8] The medulla of the adrenal which secretes the active principle, is derived from the sympathetic nervous system and with possibly a few exceptions is not represented in hypernephromas Therefore the presence of adrenalin is not to be expected in hypernephromas, since the adrenal cortex which these tumors reproduce does not normally form adrenalin. It is possible that tumors arising from the adrenal itself may be found to contain adrenalin indeed Folger[9] claims to have obtained a rise of blood-pressure in animals by injecting extracts of adrenal tumors of horses but in this case the question may be raised as to whether the adrenalin was produced by the tumor or by the remnants of the adrenal

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6 Frankel Arch f exper Path u Pharm, 1909, lx, 305
7 See Bullock and Sequeira Tr Path Soc, London 1905, lvi, 189 Thin mum Berl klm Wchnschr Jan 18 1909 xlvi 103
8 See Ohlmacher, Journ Med Research, 1902 vii, 421
9 Folger Monatschr f prakt Tierheilk, 1908 xx No 1

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JULY, 1909

FURTHER OBSERVATIONS ON THE THIRD HEART SOUND

WILLIAM SYDNEY THAYER M.D.

BALTIMORE

At the last meeting of the Association of American Physicians[1] I made a few remarks concerning the frequency especially in young people of a third heart sound heard in early diastole somewhere between one-tenth and two and one-tenth of a second after the second sound of the heart causing a character we protodiastolic gallop. This sound is especially common in the recumbent and left lateral postures and is more frequent in young individuals. It was pointed out that it was often associated with a palpable and sometimes even with a visible impulse and the impulse was shown to be identical with the normal early diastolic elevation of the apex cardiogram. Further analogies were pointed out between this sound and that which characterizes the early diastolic gallop rhythm heard under certain pathological conditions especially in aortic insufficiency, in mitral stenosis and in adherent pericardium. Cardiograms and jugular tracings showed that the ascending limb of the protodiastolic elevation of the cardiogram corresponds with the descending limb of the v wave of the jugular pulse, but when allowance is made for transmission time the apex of the protodiastolic elevation falls often on a slight rise described first by Hirschfelder as the h wave. This wave was present or indicated in a surprising proportion of my cases.

During the past six months Dr. Peabody and I have endeavored to accumulate records of different forms of pathological gallop rhythm as well as of those instances of third sound in normal individuals with the view if possible, of determining, first, the frequency of this phenomenon in the healthy man and second, its relation if any to the pathological protodiastolic gallop rhythm. While I am not ready at the present moment to enter into an extended discussion of the pathological gallop rhythms there are certain points with regard to our observations which seem to me worth bringing up to-day.

* Read before the Association of American Physicians in May, 1909

1 Thayer, W. S. The early diastolic heart sound (the so-called third heart sound) Boston Med and Surg Jour 1908, clviii, 713. Tr Assn Am Phys, 1908, xxiii, 326.

I THE FREQUENCY OF A THIRD SOUND IN NORMAL INDIVIDUALS AND THE CONDITIONS UNDER WHICH IT IS OBSERVED

We have studied a limited number of healthy patients who had entered the hospital for trivial surgical complaints, a number of normal boys and girls of different schools, as well as a series of physically healthy individuals at the city jail [2] These observations have been in some respects rather surprising I have examined altogether 231 consecutive individuals, in 65 per cent of these subjects under the age of forty the third heart sound was present This sound, however, is rarely audible in the erect posture, it is present commonly in the dorsal decubitus and is almost always clearer in the left lateral position, where the apex impulse is more evident Its frequency varies in an interesting manner according to the age of the individual The frequency with which the third sound was heard in these 231 individuals when arranged according to decades is shown by the accompanying table and chart (Fig 1)

TABLE SHOWING THE FREQUENCY OF THE THIRD HEART SOUND IN TWO HUNDRED AND THIRTY ONE NORMAL INDIVIDUALS

Decades	1	2	3	4	5	6
Cases	39	90	55	26	14	7
Percentage of cases with third sound	58 9	84 4	50 9	42 3	14	0

It may then safely be asserted that the early diastolic or third sound is a normal phenomenon in a large proportion of young individuals

A further analysis of these cases shows that in every decade except the fifth, in which there were but 14 cases, the average pulse rate was somewhat slower among the cases in which the third sound was audible than among those in which it was not heard

Cardiographic and jugular tracings have been taken in a number of cases In all instances these show a rather marked protodiastolic elevation on the cardiogram They do not, however, show as constant an h wave as was indicated in my early tracings

It may then safely be asserted that the early diastolic or third sound is a normal phenomenon in a large proportion of young individuals

II WHAT IS THE CAUSE OF THIS PHENOMENON ?

While these observations do not justify positive conclusions on this point, they have on the whole strengthened me in the feeling that was expressed last year that the sound is probably the result of a sudden tension of the mitral valve occurring with the first inrush of blood at the

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[2] For the privilege of examining these prisoners I am indebted to the courtesy and kindness of Dr G L Wilkins

beginning of diastole   As has been previously shown this sound is unquestionably coincident with the impulse associated with the first inrush of blood from auricle to ventricle   it is especially frequent in cases in which this impulse is materially marked

One might therefore expect the sound to be audible in normal individuals

Decades	1	2	3	4	5	6
No of Cases	(39)	(98)	5	(26)	(11)	(7)
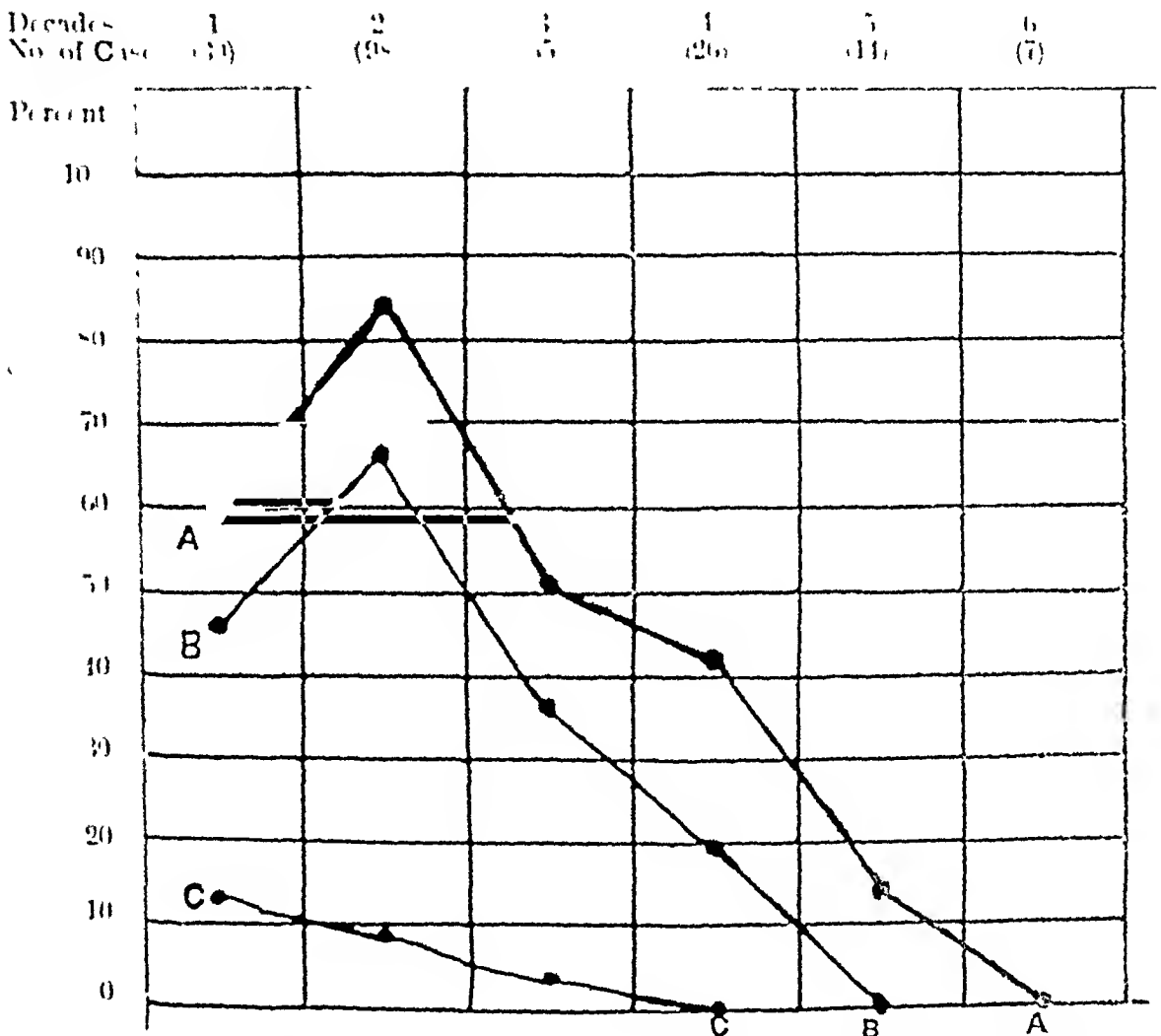
Fig 1—Chart showing occurrence of a third heart sound in normal individuals   The uppermost line (A A) indicates percentage of cases in which the sound was heard   the second (B B) line the percentage of cases in which the sound was heard in the dorsal decubitus   the lowest line (C C), the percentage of cases in which the sound was heard in the erect posture

1 In positions in which the apex is especially accessible

2 Under circumstances in which the quantity of blood in the left auricle is large

But when we consider the conditions under which the sound is heard in normal individuals we find that it is best audible

1 In positions in which the apex is especially accessible—i e on the back and left side

2 With a rather slow pulse, which means a larger volume of blood

3 During the first slow beats of expiration where, beside the influence of rate, we have the presence of more blood as a result of the increased aspiration into the lung during inspiration
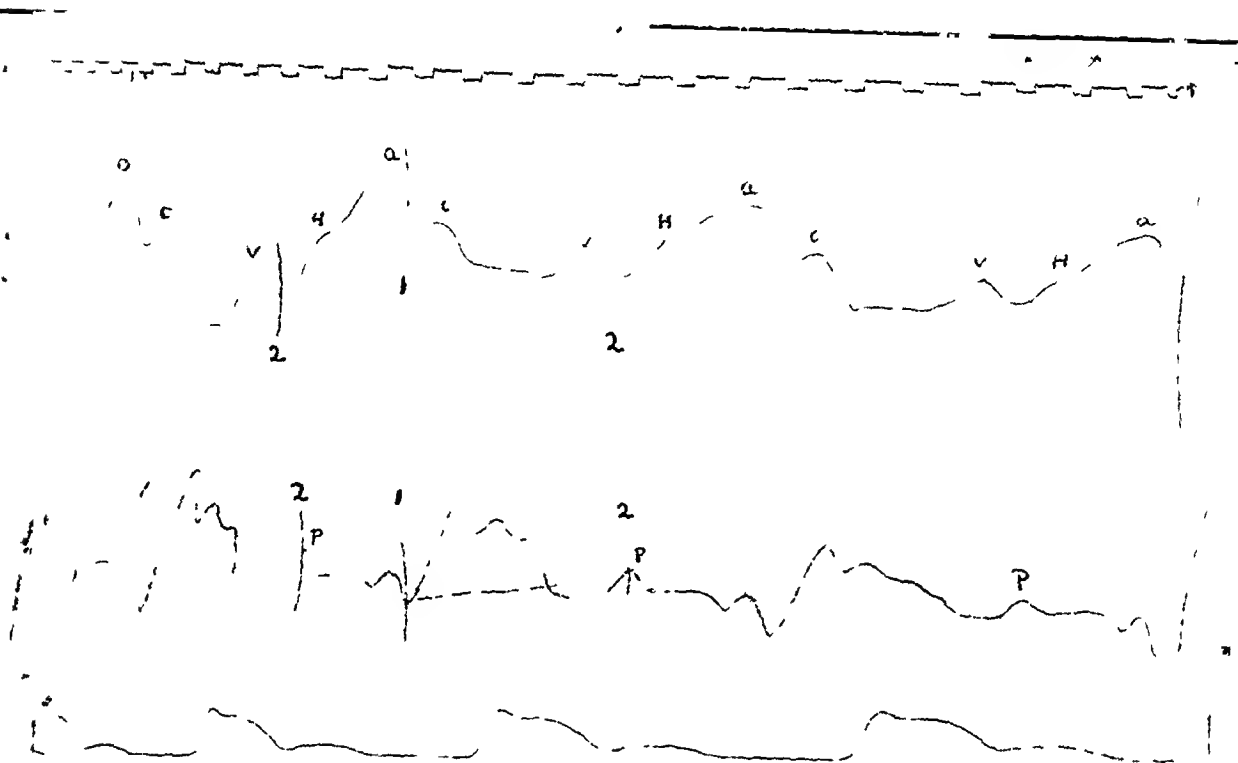
Fig 2—Third heart sound (protodiastolic gallop) Normal heart The upper tracing is from the jugular vein, the middle tracing is the apex cardiogram, the lowest tracing is from the brachial artery The timer registers tenths of seconds

Moreover, in pathological conditions one might expect the diastolic impulse and sound to be more marked

(a) In conditions in which the quantity of blood entering the ventricle in diastole is exceptionally large

(b) Where the filling of the ventricle is unusually rapid

(c) Where the ventricle, owing to changes in the walls or a diminished vascular tonus, is unusually distensible or dilated

Now (a) the conditions under which an increased quantity of blood enters the ventricle in diastole are especially aortic and mitral insuffi-

have been long in the recumbent posture is due to the fact that a large amount of venous blood has accumulated in the splanchnic vessels

In cases of dilatation of the left ventricle, which are commonly associated also with a relative mitral insufficiency, the condition is, as is well known, especially common In all these conditions, with the presence of gallop rhythm, the protodiastolic elevation on the cardiogram is marked

With regard to mitral stenosis, in which, as is well known a third sound is very common, the condition is not always analogous In some
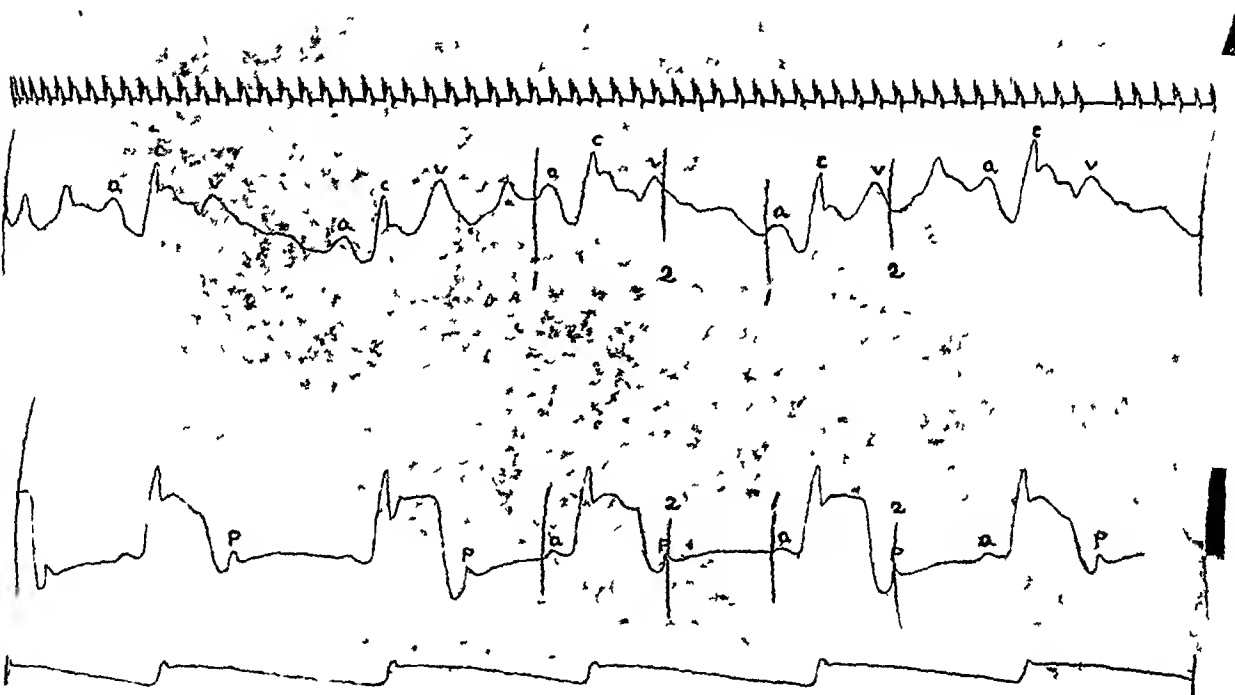
Figure 4 —Protodiastolic gallop rhythm Mitral insufficiency The uppermost tracing is from the jugular vein, the middle tracing is the apex cardiogram, the lowest tracing is from the brachial artery

cases associated with insufficiency in which the stenosis is not of high degree, the conditions, as has been pointed out, are such that similar manifestations might be expected, and this is the case In others an opening snap, occurring apparently rather early is audible without a definite protodiastolic shock In cases of extreme stenosis it is possible that the tension of the valves giving rise to the sound may occur as a result of pressure from above in association with the diastolic relaxation of the ventricle as was suggested by Potain With this exception, however it seems highly probable that the normal and pathological early dias-

tolic sounds are due to a similar phenomenon, at least in the great majority of cases. This is borne out by the similar character of the sounds and their relation to the cardiogram and the jugular pulse.

III. WHY IS IT THAT THE SOUND IS SO MUCH BETTER HEARD IN THE RECUMBENT POSTURE AND ON THE LEFT SIDE?

Is it simply because of the greater accessibility of the apex? This seems to me hardly possible. If, however, we adopt the working hypothe-

Figure 5.—Protodiastolic gallop rhythm. Mitral insufficiency. The uppermost tracing is from the jugular vein, the middle tracing is the apex cardiogram, the lowest tracing is from the brachial artery.

sis that the sound is due to a sudden early diastolic tension of the mitral valve, its greater frequency in the recumbent posture might easily be explained by the increased quantity of blood which must reach the left heart in this position owing to the more favorable conditions for venous flow. In connection with this question I have the distinct impression that the sound is more marked in individuals who have been in the erect posture and who lie down for the examination than in those who have been longer in the recumbent posture. In these cases the venous flow to the heart may well be increased on the first change of position owing to

the elevation of the extremities, an increase which, after a time, might disappear as a result of the accumulation of blood in the abdominal vessels. In a few cases I have compared the heart sounds of patients in the dorsal decubitus with those heard when the legs and arms were held by attendants in an elevated position. The elevation of the extremities has seemed to me distinctly to increase the intensity of the sound

Figure 6 —Protodiastolic gallop rhythm. Mitral and aortic insufficiency. The uppermost tracing is from the jugular vein, the middle tracing is the apex cardiogram, the lowest tracing is from the brachial artery

IV. WHY SHOULD THE SOUND BE MORE MARKED IN THE LEFT LATERAL POSTURE?

The answer to this would seem to be simple enough. The slight and almost constant difference between the frequency with which the sound is heard in this position and in the dorsal decubitus may well be accounted for by the greater accessibility of the apex and by the fact that the entrance of blood into the ventricle does not in this position take place against gravity

In addition to this it may be that the apex systolic murmur so commonly heard in young individuals in the recumbent and especially in the

left lateral posture, in perfectly normal hearts, may represent, in some instances a slight functional mitral insufficiency, in which case the greater frequency of the sound in these positions would be easily explicable

In conclusion these observations would seem to justify the following assertions:

1 The third heart sound is present in the majority of young individuals in the recumbent and left lateral posture

2 This sound may well be due, as first suggested by Hirschfelder and later, independently, by Gibson and myself, to the sudden tension of the auriculoventricular valves as a result of the first rush of blood from auricle into ventricle in diastole

3 Pathologically the sound is especially frequent in conditions in which the quantity of blood entering the ventricle from the auricle is especially large, in which the diastole is unusually rapid, in which there is a lowered muscular tonus or dilatation of the ventricle The most striking examples of these conditions are aortic and mitral insufficiency, some instances of slight mitral stenosis combined with insufficiency, adherent pericardium, myocardial weakness and dilatation of the ventricle

4 A protodiastolic gallop, therefore, is not necessarily a pathological manifestation

106 Cathedral Street

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406 Cathedral Street.

THE EFFECT OF TUBERCULOSIS ON THE HEART *

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A good heart is one of the best assets possessed by a patient suffering from pulmonary tuberculosis From the earliest infection by the tubercle bacillus it is more or less disturbed in its action, and as the focus of infection grows larger the effect on the heart becomes greater The deleterious influences which react on the heart are many and from varied sources The heart problem increases in complexity as well as in importance as the disease advances in severity While it would seem that, with the present-day knowledge of tuberculosis and the means at our command for making an early diagnosis, we should see a greatly diminished number of cases of advanced tuberculosis in the future, yet I fear that it will be a long time before tuberculosis will be generally diagnosed early, and I do not doubt that any knowledge that may be added bearing on the condition of the heart in advanced infections will be welcome and of clinical value

There are many difficulties in the way of giving an opinion on the condition of the heart in individuals suffering from tuberculosis, especially those suffering from advanced tuberculosis The position of the heart in the chest is altered, the pulmonary circulation is embarrassed, changes occur in the systemic arteries as well as the heart itself, blood pressure is altered, the relative intensity of the heart tones is changed, numerous murmurs appear at the various valve areas and numerable adventitious sounds are heard Without bearing these facts in mind many erroneous opinions will be given

The first change that occurs in the heart and circulatory system is noted as soon as the infection is of sufficient grade to cause clinical symptoms This is an acceleration of the pulse It is probably of toxic origin and is associated with a lowering of the blood pressure due to the action of the tubercle toxins on the vasodilators This quickening of the pulse may be slight, in which case it would perhaps be noted only after exertion, or it may be marked and even show when the patient is at rest The causes which operate to quicken the pulse during the course of pulmonary tuberculosis are many The rapidity is in

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*Read before the Sixteenth International Medical Congress, Budapest, Hungary, Aug 29 to Sept 4, 1909

part doubtless a physiological response on the part of the heart to compensate for the lowering of the blood pressure caused by the dilatation of the arterioles. in part due to a lack of power on the part of the heart muscle itself resulting from the action of toxins or because of overwork. in part due to a stimulation of the sympathetic fibers in the chest and doubtless in part due to the interference with the inhibitory action of the vagus

As the disease progresses and the action of the toxins becomes more manifest. general muscular wasting occurs in which the heart muscle bears its share Then it is that we find the greatest changes in the blood pressure Opposing the fall in pressure we find, early in the disease. hypertrophic changes in the right ventricle. and later, quite often, a thickening of the arterial walls

Having noticed a thickening of the arterial walls in many cases of advanced tuberculosis I decided to find out how general it is, with the result as noted in Table 1 In the first place, I found it most commonly in patients who had suffered from the disease for many years, consequently in those in whom the fibroid form of the disease predominated I do not doubt that the cause is the prolonged action of work toxins on the vessel walls This opinion is supported by Table 1, which shows the comparative frequency of palpable arteries in those ill less than one year. from one to two years and more than two years.

TABLE 1 — SHOWING THE COMPARATIVE NUMBER OF PALPABLE RADIALS IN PATIENTS WHO HAVE HAD ILL LESS THAN ONE YEAR, ONE TO TWO YEARS AND MORE THAN TWO YEARS Total Number of Patients 162

Condition of Radials	Duration of Disease		
	Less Than 1 Year	1 to 2 Years	More Than 2 Years
Palpable	11	26	60
Non palpable	11	21	3

I took as an index to the condition of the arterial walls the condition of the radials, and determined whether or not they were palpable either after stripping the vessel from below upward with the second finger of one hand and from above downward with the second finger of the other hand and then using the first finger to do the palpating of the empty vessel. or by palpating the vessel while the blood was shut off from the artery by the cuff of the blood pressure apparatus Very inexact data will be obtained unless the column of blood is first expressed from the artery.

Analyzing the blood pressures of the 162 cases here represented, we see that there were 11 first-stage cases with an average pressure of systolic

1 Stanton's sphygmomanometer was used in making the blood pressure observations recorded in this report The average blood pressure of 20 healthy adults taken under the same conditions showed systolic 130, diastolic 110

108, diastolic 78; 21 second-stage cases with an average pressure of systolic 108, diastolic 81, and 130 third-stage cases with an average of systolic 103, diastolic 75. It must be remembered that these pressures were taken in Southern California, where climatic conditions favor a relatively low pressure. If we note the influence exerted by the palpable arteries (we include only the 130 cases in Stage III), we shall see that the average pressure in the 83 cases in which the arteries were palpable was: systolic 105, diastolic 76, while that of the 47 cases where they were not palpable was: systolic 102, diastolic 75. That this condition of the arteries is not influenced largely by the age of the patients is very evident from Table 2, for of those who had palpable arteries none were between the ages of 15 and 20; 21 between 20 and 30, 45 between 30 and 40; 20 between 40 and 50, and 7 between 50 and 65. And of those whose arteries were not palpable 11 were between the ages of 15 and 20; 35 between 20 and 30; 16 between 30 and 40, 6 between 40 and 50, and 1 between 50 and 65

TABLE 2—CONDITION OF THE ARTERIES ACCORDING TO AGE

Conditions of Arteries	15 to 20 Years	20 to 30 Years	30 to 40 Years	40 to 50 Years.	50 to 65 Years
Radials Palpable	00	21	45	20	7
Radials not Palpable ..	11	35	16	6	1

Now, if we note the effect exerted by myocarditis (in this class I placed only those who showed marked clinical signs), we shall note the opposite effect. The average pressure in the 62 cases in the third stage showing myocardial change was: systolic 97, diastolic 70; while the average pressure in the 68 which did not show this change was: systolic 110, diastolic 82

Further analysis of these cases seems to indicate that these two factors, thickening of the arterial walls and degeneration of the heart muscle, are two very potent factors in modifying the blood pressure in tuberculous patients. Table 3 shows this very plainly for the cases which did not show myocarditis. Where myocarditis was not present, those patients who had palpable radials had a blood pressure of systolic 113, diastolic 82, even higher than the pressure of the first- and second-stage cases. In those of the same class whose radials were not palpable the blood pressure was, systolic 105 diastolic 83 making a difference of about 8 points in the systolic pressure, which seems to be due to the condition of the arteries as determined by the radials. This difference, although present, is not apparent in the cases showing myocardial change as arranged in Table 3. If Table 4 is studied, however, it will be seen that the reason for those who have palpable radials and myocarditis having a lower blood pressure than those whose radials did not show

the change is that several of the former had such severe myocardial change that the tendency to raise the pressure owing to the changes in the arteries was overcome and the actual pressure was lowered. This might indicate also that this thickening of the arteries, while helping to maintain the blood pressure in an earlier stage of advanced tuberculosis finally proves detrimental in that it causes too great a strain to be thrown on the heart, and the heart muscle being unable to meet the demand, fails.

TABLE 3.—Showing the Effect of the Condition of the Arteries Wall on Blood Pressure when Ascertained with the Oscillating Pressure.

	No.	Average	No.	No. Average
Radials		Systolic	Diastolic	Systolic Diastolic
Radials Palpable	11	87	70	42	117	8
Radials Non-palpable	21	95	64	26	105	8

Myocardial change is present in some degree in practically all cases of tuberculosis. In the earlier stages of the disease, when the patients' general condition is good, this condition is chiefly part of the overworked ventricle to enable it to do the extra work caused by the extra demand of the pulmonary vascular area. Later, through the action of the toxins, the general malnutrition, overwork and other depressing causes, the muscle degenerates and weakens. The field of action is progressively diminished and whereas at first the heart is able to perform its function by calling on its reserve energy and strength of its muscle, a power evidenced by the hypertrophy which takes place, it is no longer able to do so, and as a result the circulation is curtailed and superficial, and dyspnea and cyanosis appear.

In determining the presence of myocardial change, I took into consideration both clinical symptoms and signs on the part of the heart itself, and designated as cases of myocarditis only such heart as showed marked change.

There are many difficulties in the way of forming an opinion on the heart in advanced tuberculosis. In the first place, we do not have the same anatomical relations in advanced tuberculosis as we do in the normal chest. Through the effect of pleurisy, contraction and compensatory emphysema the heart is often displaced and the heart valves no longer bear their normal relation to the superficial landmarks. If the heart is uncovered by the retraction of a portion of the lung, sounds that are not at all intensified may appear much louder than they would under normal conditions, and, on the other hand, if a large portion of emphysematous lung be interposed between the heart and chest wall the sounds will appear much weaker than they really would with normal covering, and it would be very difficult to accurately judge their intensity.

The presence of infiltrations and cavities also alter the quality and apparent intensity of the sounds It can readily be seen, then, that it is difficult to compare and determine the relative intensity of the sounds at the different valve areas

In making the observations recorded here I was compelled to disregard entirely the usual location of the valve sounds on the surface of the chest because the hearts were displaced to one or the other side in many instances My data on the various valves was taken at the point where it seemed that the valve in question would most probably be located when the shifting of the heart had been considered

The following observations were made with the stethoscope

Apex—
    Weak, 7 times
    Strong, 5 times
    Double, 89 times
    Gallop rhythm, 17 times
    Bruit, organic 6, functional 11 times
    Triple sound, 1
    Irregular, 2
Aortic—
    First sound weak, 21 times
    Second sound accentuated, 72 times
    Second sound weak, 5 times
    Bruit, systolic 6, diastolic, 4, organic, 5, functional, 5
Pulmonic—
    First weak, 18 times
    Second accentuated, 94 times
    Second double, 35 times
    Bruit, 6 times
Tricuspid—
    Insufficiency, 4 times
Adventitious Sounds—
    Probably pleuropericardial adhesions, 15 times
    Pericarditis, 1 time
    Pericarditis (adhesive) 3 times

Some of the observations mentioned above require explanation because the personal element always comes into play in characterizing observations of this kind Errors of judgment are prone to creep in, but a few words of explanation will doubtless make the meaning clear

A double beat was observed at the apex in 89 of the 162 patients I designated as double what I considered as a departure from the normally recognized firm tone of the apex The degree of doubling varied a great deal from what might be considered as a slight impurity to two very distinct sounds It is estimated that a double sound at the apex is heard in about 10 per cent of normal hearts, but it will be seen that in the patients here reported it occurred in more than 50 per cent of the cases

The frequency with which accentuation of the second aortic was found also requires explanation. In some cases this might be produced by the thickening of the systemic arteries; in others, it is only apparent and not actually an accentuation, the apparent accentuation depending on the nearness to infiltrations and cavities; in some cases it is due to the fact that the valve is uncovered and consequently seems louder and more accentuated than it is.

Three of the bruits designated as organic occurred in one family.

The four cases of tricuspid insufficiency were due to advanced degree of degeneration and dilatation of the heart muscle.

During the course of this investigation my attention was called to the Bock stethoscope as offering help in determining the relative intensity of the heart sounds. I regret that I did not have the Bock record in all instances, but I have tried it in a sufficient number of cases to demonstrate its value. By studying Table 1 it will be seen that the Bock readings give a fair estimation of the condition of the heart muscle. In interpreting the Bock readings it must be remembered that the standard is an arbitrary one and the readings of each heart must be considered alone. Bock has determined that for the normal individual the aortic sound should be about one-third louder than that heard at the apex and the pulmonary sound from five to fifteen points below the aortic.

Another very important topic for consideration in discussing the heart in its relation to advanced tuberculosis is the effect produced on it by the displacement which occurs on account of the changes in the lung and pleura. That this has received too little consideration in the past is self-evident.

It is natural to suppose that organs perform their functions best when in their natural positions. The heart in its normal position lies on the diaphragm and swings from the great vessels which serve as points of fixation at the base. It is surrounded and limited in its motion by the pericardium and the amount of motion allowed the heart is dependent, to a certain extent, on the size of the pericardium. The pericardium is fixed at five points: to the under surface of the sternum, to the diaphragm, to the right and left pleurae and to the great vessels of the chest. The heart is allowed slight motion within the pericardium under normal circumstances, as is noted on the change of position from lying on one side to lying on the other. Changes of this character in no wise interfere with the heart in the performance of its function because the position and size of the pericardium is not changed, the large vessels are lying free and easy in their normal place and no impediment is offered to the free and natural movements of the heart itself or to the

TABLE 4—EFFECT OF TUBERCULOSIS ON THE HEART

Sex	Stage, Turban	Age	Duration of Illness Yrs	Involvement †	Blood Pressure Systolic	Blood Pressure Diastolic	Radialis *	Position of Heart — Fourth Interspace R Cm	Position of Heart — Fourth Interspace L Cm	Diameter	Heart Tones — Mitral	Heart Tones — Aortic	Heart Tones — Pulmonic	Heart Tones — Tricuspid	Adventitious Sounds	Heart Muscle	Remarks	Bock Apex	Bock Aortic	Bock Pulmonic
F	I	26	3	R > L	115	82	—	3.75	6.25	10	1st double							85	62	62
F	"	18	1½	L > R	115	84	—	3.5	4.5	8	Slight gallop rhythm							82	75	80
M	"	32	1½	L > R	100	74	+	3.0	7.0	10		2d accent	2d accent							
M	"	18	5½	R > L	95	65	—	3.0	6.25	9.25		2d accent	2d accent							
F	"	20	½	L > R	110	72	—	2.25	6.75	9		Systolic murmur organic								
M	"	26	2½	L > R	125	100	—	3.75	8.0	11.75										
M	"	13	1	L > R	88	55	—	2.5	5.5	8.0										
M	"	21	3	L > R	132	74	—	3.75	7.0	10.75		2d accent								
L	"	22	13	R > L	98	70	—	2.75	7.0	9.75										
M	"	29	½	L > R	124	112	+	3.25	10.5	13.75										
F	"	34	1	L > R	112	77	—	4.0	7.0	11.0	Double	2d accent						80	55	55
M	"	21	2	L > R	96	69	+	4.0	7.87	11.87			1st weak					80	70	65
M	"	31	7	R > L	130	113	+	3.75	5.5	9.25		2d accent						72	60	64
M	"	30	3	L > R	113	111	—	3.75	7.0	10.75								70	55	65
L	"	29	1½	L > R	111	108	—	2.75	8.0	10.5	Systolic bruit (functional)							65	55	35
M	"	22	1/6	L > R	108	86	—	3.5	7.0	11.0	Systolic bruit (functional)		2d accent					85	70	65
M	"	21	1½	L > R	120	112	—	3.0	8.0	9.25			Systolic bruit (functional)					85	75	70
L	"	17	1½	R > L	112	83	—	3.5	5.75	8.75						Pleuropericardial adhesions		90	72	70
L	"	11	1½	R > L	98	69	—	4.5	4.25		Systolic bruit (functional)		2d accent					73	60	67

* In this column + stands for "palpable", — for "non-palpable", L > R, left lung involvement greater than right

† R > L, signifies right lung involvement greater than left; L > R, left lung involvement greater than right

TABLE 4 — EFFECT OF TUBERCULOSIS ON THE HEART (Continued)

Sex	Stage, Turban	Age	Duration of Illness Yrs	Involvement	Blood Pressure Sys-tolic	Blood Pressure Dias-tolic	Radials	Position of Heart Fourth Interspace R Cm	Position of Heart Fourth Interspace L Cm	Position of Heart Diameter	Heart Tones Mitral	Heart Tones Aortic	Heart Tones Pulmonic	Heart Tones Tricuspid	Heart Tones Adventitious Sounds	Heart Muscle	Remarks	Bock Apex	Bock Aortic	Bock Pul-monic
F	III	36	2	L > R	90	68	+	2.75	8.0	10.75	1st double	1st weak, accent 2d accent	2d 1st weak, 2d accent 2d accent					85 75	65
F	"	17	9	R > L	95	58	–	1.0	6.5	10.5	1st double	2d accent				Myocarditis		75 65	15
M	"	22	1	L > R	108	76	+	2.75	10.0	12.75	1st double		2d accent metallic 2d double					92 70	75
F	"	37	1	L > R	100	70	+	3.75	3.75	12.5	1st double		2d double		Pleuropericardial adhesions	Myocarditis			
M	"	38	4	L > R	98	72	+	2.75	8.0	10.75	Double	2d accent	2d double accent 2d accent			Myocarditis		65 63	70
M	"	30	2	R > L	108	76	+	5.0	4.5	9.5	1st double	2d sl accent						83 75	77
F	"	36	2	R > L	115	78	–	4.5	6.5	11.0	1st double	2d accent	1st weak					80 75	75
M	"	21	1½	L > R	88	54	+	3.5	8.0	11.5	1st double	2d accent	2d accent			Myocarditis		67 50	30
M	"	36	3	L > R	122	83	+	3.75	5.75	9.5	Double	1st weak	1st weak					65 70	55
F	"	39	2	L > R	87	63	+	1.5	11.0	12.5	1st double,	2d accent	2d accent			Myocarditis			
F	"	38	2	L > R, R	116	88	–	0.5	8.5	9.0	1st weak	1st very weak	1st very weak	Insufficiency		Myocarditis		80 70	70
M	"	31	1	R > L	100	72	+	6.5	7.75	14.25	Double	2d double accent				Myocarditis			
L	"	29	1	R > L	80	58	–	5.25	1.25	9.5	Gallop rhythm	2d sl accent	2d accent			Myocarditis			
M	"	31	1½	L > R	100	75	+	2.0	9.0	11.0	Bruit systolic organic	2d metallic accent				Myocarditis			
M	"	29	3	R > L	122	86	+	3.75	7.5	11.25	1st double, systolic murmur (functional)	Systolic murmur (functional)				Myocarditis	Nephritis	80 75	72
L	"	30	1½	L > R	95	77	+	2.25	6.75	9.0	1st double								
M	"	20	7½	L > R	101	71	–	1.0	6.75	10.75	1st double	1st weak, 2d weak	2d double			Myocarditis			
M	"	17	2	R > L	106	80	+	1.5	5.5	10.0						Myocarditis		82 72	60

TABLE 4.—EFFECT OF TUBERCULOSIS ON THE HEART (Continued)

Sex	Stage, Turban	Age	Duration of Illness yrs	Involvement	Blood Pressure Systolic	Blood Pressure Diastolic	R radials	Position of Heart Fourth Interspace R Cm	Position of Heart Fourth Interspace L Cm	Diameter	Mitral	Aortic	Pulmonic	Tricuspid	Adventitious Sounds	Heart Muscle	Remarks	Bock Apex	Bock Aortic	Bock Pulmonic
M	III	10	10	L>R	88	55	+	2.5	8.5	11.0	Weak, 1st double; 1st double	1st 2d sl accent	2d double met allie	Systolic bruit						
F	"	25	1	R>L	112	80	−	2.5	6.0	8.5	Gallop rhythm; 1st double	Diastolic murmur (org'ic); 2d double accent	2d accent			Myocarditis				
F	"	10	3	L>R	85	63	−	2.0	10.0	12.0	1st double	2d accent	2d accent							
M	"	20	2½	R>L	108	74	+	1.0	6.5	10.5	1st double	2d accent	2d accent			Myocarditis				
F	"	35	1	L>R	96	66	+	3.75	8.75	12.5	1st double	2d accent								
M	"	20	3	L>R	92	64	−	1.75	9.0	10.75	1st double			Relative insufficiency		Myocarditis	Adhesive pericarditis, nephritis			
M	"	15	1	L>R	91	69	−	2.0	7.25	9.25	1st double	2d accent met allie	2d accent double							
M	"	63	~	R>L	65	75	+	2.0	8.0	10.0	1st double	2d accent met allie	2d accent							
F	"	33	2	R>L	96	60	−	4.75	7.5	10.25	1st double		2d sl accent							
F	"	11	2	R>L	98	58	+	2.0	7.5	9.5	1st double	2d accent	2d accent			Myocarditis				
F	"	36	2	L>R	92	62	−	3.5	6.5	10.0	Double		2d double			Myocarditis				
M	"	29	½	L>R	100	80	+	5.5	6.0	11.5	1st double	2d accent double	2d accent double			Myocarditis				
M	"	21	6	R>L	111	85	+	1.75	9.25	11.0	1st double	2d accent double				Myocarditis				
M	"	65	3	L>R	135	100	+	0.0	12.5	12.5	1st double	2d accent	2d accent							
M	"	47	3	R>L	106	71	+	1.0	9.0	13.0	1st double	1st weak, double	2d accent				Arterio sclerosis			
M	"	20	½	L>R	100	70	−	4.0	7.0	11.0	1st double, gallop rhythm		2d accent							
F	"	38	7	R>L	106	72	+	0.75	10.5	11.25		2d accent	2d accent		Pleuropericardial adhesions	Myocarditis				
F	"	28	1	L>R	92	56	−	0.75	8.75	9.5	1st double	2d accent	2d accent double				Pericarditis			

TABLE 4.—EFFECT OF TUBERCULOSIS ON THE HEART (Continued)

Sex	Stage, Turban	Age	Duration of Illness Yrs	Involvement	Blood Pressure Systolic	Blood Pressure Diastolic	Radials	Position of Heart Fourth Interspace R Cm	L Cm	Diameter	Heart Tones Mitral	Aortic	Pulmonic	Tricuspid	Adventitious Sounds	Heart Muscle	Remarks	Bock Apex	Aortic	Pulmonic
M	III	19	9	L > R	92	60	+	-1.5	12.0	10.5	1st double, 2d accent	2d double accent					Arterio sclerosis			
M	"	20|18	18	L > R	92	60	+	1.0	12.0	13.0	1st double	1st accent metallic	2d accent			Myocarditis				
F	"	11	2	R > L	105	82	+	1.0	6.0	10.0	Systolic brut (organic)	Systolic mur (org.) 2d accent	2d accent			Myocarditis				
M	"	33	3	R > L	122	95	+	3.75	7.5	11.25		2d accent	2d sl accent							
M	"	32	½	R > L	102	77	+	5.0	7.5	12.5	Gallop rhythm		2d double 2nd accent							
F	"	33	1	R > L	98	61	-	5.0	7.0	12.0		1st weak, 2d accent				Myocarditis	Nephritis			
M	"	11	1½	L > R	115	85	+	1.25	7.25	11.5		2d accent	2d accent							
F	"	10	1	L > R	110	71	+	1.0	10.0	11.0	1st double	2d accent								
F	"	10	3	R > L	110	80	-	4.5	5.5	10.0	1st double									
M	"	33	3	R > L	120	95	+	5.0	6.5	11.5	1st double	1st weak, 2d accent	2d / 1st weak, 2d accent		Pleuropericardial adhesions	Myocarditis, dilatation		82|70	70	75
F	"	42	2	L > R	108	90	+	1.5	10.5	15.0	1st strong double		2d double			Myocarditis dilatation		85|10		50
F	"	21	2	R > L	90	66	+	4.0	9.0	13.0			2d sl accent					88|60	65	65
F	"	31	3	L > L	97	68	-	2.75	7.75	10.5	1st double		2d accent					77|75	75	75
F	"	25	1	L > L	87	62	+	1.75	9.5	11.25	1st double gallop rhythm	1st weak, 2d double / 2d metallic	1st weak, 2d double			Myocarditis		65|65	70	70
M	"	33	2	R > L	108	78	+	1.5	7.5	12.0	1st double		Systolic brut, 2d double			Myocarditis		70|62	55	55
F	"	10	2	R > L	106	71	+	2.0	6.5	8.5	1st double	2d accent						85|75	75	75
F	"	31	1½	L > R	107	77	+	3.0	10.25	13.25	1st double gallop rhythm		1st weak, 2d dbl accent			Myocarditis dilatation		75|65	65	65
F	"	17	3	L > R	96	66	-	1.5	6.5	11.0	1st double		1st weak, 2d accent					77|75	75	75

outflow of blood in the vessels When, owing to contraction of one or both lungs, traction is made on the pericardium through its attachments with the pleura, a very different condition is brought about and the heart is forced to work at a great disadvantage This can be readily understood if we take an extreme case in which the heart has been drawn up and out until the apex is found in the left axilla owing to marked contraction of the left upper lobe and compensatory emphysema of the right lung In such a case we must assume that the pericardial space is encroached upon, thus interfering with the free movements of the heart itself The traction of the pericardium on the vessels not only changes them from their natural position, but bends them in their course and thus throws an extra amount of work on the heart What is true in this extreme case is also true in those of less degree, but to a less extent For the heart to perform its function under these difficulties would tax a heart muscle of normal power, but, in cases like these, the heart muscle is perhaps always the seat of degenerative change and consequently less able to meet the increased work thrown upon it

In determining the deep cardiac dulness in order to estimate the size of the heart, I found considerable difficulty In the first place, it is very difficult to percuss the deep borders with accuracy The degree of error may be reduced to a minimum, however, by the employment of several different kinds of percussion to check each other I used two or more of the following methods in each case finger-finger percussion, Ebstein's percussion, rubber-tube percussion and auscultatory percussion

There is some doubt as to what should be considered the normal limits of the normal heart Of course, this differs according to the age and size of the individual and size and shape of the chest Reiss[2] gives the following measurements from averages taken from a number of medium-sized individuals

Distance of right border of heart from median line, third interspace, 2 75 cm , fourth interspace, 3 75 cm

Distance of left border of heart from median line, third interspace, 4 75 cm , fourth interspace, 7 5 cm

Sahli,[3] commenting on these measurements, says that they make the heart too small If we take these measurements as a standard however it will be seen that a large percentage of the hearts in patients suffering from advanced tubcreulosis are displaced Of the 162 hearts examined, 58 were in practically the normal position, 27 were displaced to the right and 77 were displaced to the left Of the Stage I cases one was displaced and 10 were in normal position Of Stage II cases 4 were

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2 Reiss   Ztschr f klin Med , 1888, xiv, 12
3 Sahli   Diagnostic Methods, Philadelphia, 1905

7 In the majority of advanced cases (99 out of 130) the heart is displaced and working at a disadvantage

8 In estimating the size of the heart it must be remembered that as the heart pushes over to the left it pushes backward and consequently the lateral diameter as taken on a level with the fourth interspace does not give an adequate idea of the real or true size of the heart, also that the hypertrophy of the right heart often throws the left ventricle backward, producing the same result

INFLUENZAL MENINGITIS

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While the question of the relation that Pfeiffer's bacillus bears to influenza or "grip" may be considered an open one, the pathogenicity of this organism is strikingly demonstrated by its occasional occurrence in pure growth in the meningeal exudate in cases of meningitis Such a case, illustrating the fact that this organism at times may be highly pathogenic and presenting certain other interesting features, is here described

REPORT OF CASE

The clinical history furnished by Dr F Churchill and Dr C B Reed, is as follows

Patient —Male child, one of twin brothers, each weighing 7 pounds, born Oct 3, 1908 The mother had borne nine children and was in perfect health before the present delivery, which was normal and at full term Other members of the family were also well The baby was put to the breast eleven hours after birth, fed every three hours and did well until the morning of October 8, when the bowel movements were green and contained mucus and curds The next day the child moaned constantly and on the 10th refused to nurse at 6 a m and was dull and drowsy during the day On the 11th a "sinking spell" occurred in the morning and the patient became cold and cyanotic

Examination —At this time a physical examination was made by Drs Churchill and Reed The development and nutrition were good, color dusky The baby was quiet and relaxed but appeared drowsy The result of the examination of the head, chest, abdomen and limbs was negative Rigidity was not present and no signs suggesting meningeal irritation appeared

On October 12 the "sinking spells" continued and early in the morning general twitchings occurred, but no actual convulsions They continued through the day, together with the marked cyanosis and comatose condition Death occurred at 5 p m on the ninth day after birth and on the fourth day of the disease The temperature from October 9 to October 12 ranged between 101 8 and 104 5 F

The twin brother was healthy at birth and continued so until October 8, when he began to have numerous bowel movements, followed the next day by a continuous temperature At noon, October 11, twitchings began which continued for seventeen hours His condition grew gradually worse and death occurred on October 15, seven days after the onset No autopsy

Autopsy —In the first case a postmortem examination was made seventeen hours after death

Following is the anatomic diagnosis Acute catarrhal gastroenteritis, acute purulent lepto meningitis, acute parenchymatous, degeneration of the heart, liver and kidneys, acute swelling of the spleen, multiple ecchymoses of the pleura and thymus

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The body was very cyanotic and postmortem rigidity was not present In the abdominal cavity a few drops of yellow fluid occurred but the peritoneal surfaces were smooth and glistening No evidence of omphalitis In the pericardium there were about 2 c c of clear fluid and the pleural cavities were free On the surface of the thymus a few small ecchymoses, pin head in size, occurred, and similar hemorrhages were found on the pleural surfaces The lungs and bronchi were normal The mucosa of the stomach and intestine was red throughout and in the ileum and large bowel were small hemorrhagic spots, pin head in size The myocardium, liver and kidneys showed acute degeneration, the adrenals, pancreas, gall bladder, urinary bladder and genital organs presented no noteworthy changes The mesenteric lymph glands were soft and slightly enlarged

Over the entire convex surface of the brain were well-defined areas of greenish-yellow, friable, purulent exudate, irregular in shape and from one to several sq cm in size and 1 to 5 mm thick Between these areas the |meninges appeared smooth and transparent At the base, especially in the region of the optic chiasm and the pons and along the larger blood vessels the deposit was more abundant and diffuse and from 1 to 5 mm in thickness The blood vessels everywhere were engorged and usually, especially at the base, surrounded by the abundant exudate The ventricles were not dilated and the fluid was clear In the spinal canal a large amount of turbid purulent exudate occurred about the cord No pathological changes were present in the nasal sinuses or in the tympanic cavities

Bacteriological Examination—Meningeal Exudate Inside and outside the polynuclear cells were enormous numbers of small Gram negative polar staining bacilli Some of the cells were packed with these bacilli, but none were found in the mononuclear or endothelial cells Cultures on blood agar plates gave, in twenty-four hours, an abundant growth of small dewdrop like colonies in every way characteristic of *Bacillus influenzæ* One other colony, a staphylococcus and evidently a contamination, appeared on one of the plates, and about this was observed a cluster of larger influenza colonies indicating the symbiotic property characteristic of this organism In the fluid obtained from the spinal canal the bacilli were likewise found in pure growth and in very large numbers

Heart's Blood In the heart's blood were found on culture a few colon bacilli Repeated attempts to isolate influenza bacilli on pigeon blood agar failed The pericardial fluid was sterile

Peritoneal Fluid In smears a few polymorphonuclear cells, many small mono nuclear cells and a few Gram negative polar staining small bacilli were found Cultures on blood agar plates gave numerous typical influenza colonies Three or four colonies of colon bacilli appeared on the plate also, and about them occurred the characteristic cluster of larger influenza colonies

To summarize, in the meningeal exudate about the brain and spinal cord and in the peritoneal fluid were found influenza bacilli in large numbers and in pure growth The few colon bacilli in the peritoneal fluid and heart's blood and the staphylococcus colony in the culture from the meningeal exudate were undoubtedly contaminations and may be disregarded

Morphologically and culturally the bacilli isolated from this case corresponds to the typical influenza bacillus isolated from other sources On media other than hemoglobin media no growth takes place and on pigeon-blood agar it grows profusely The tendency to form threads while evident, is not marked Polar staining with methylene blue is distinct and dilute carbolfuchsin stains the bacillus uniformly

Pathogenicity   A few drops of exudate obtained from the base of the brain were injected into the peritoneal cavity of a guinea-pig with no results   A second guinea-pig inoculated intraperitoneally with growth from two blood-agar slants died in thirty-six hours   Examination showed a purulent peritonitis and light salpingitis   In the peritoneal pus were many leucocytes and bacilli, some of the latter being intracellular and in cultures numerous influenza colonies appeared with a few colonies of *B coli*   Pure growths of *B influenzœ* were obtained from the heart's blood, pericardial fluid, both pleural fluids and the right Fallopian tube

Two guinea-pigs, inoculated subdurally with a few drops of a dense suspension of the bacilli, died within twenty-four hours   The meninges in one were bloody but an exudate did not appear   The bacilli were recovered from the surface of the cortex and from the base of the brain, but from no other part of the body   In the second animal the meninges were congested 'but no exudate was evident   Bacilli were found in the meningeal fluid as in the first animal, but not in other parts of the body   Three guinea-pigs, inoculated with this organism behind the eyeball into the orbit, developed no symptoms other than a slight conjunctivitis   One of the animals, killed five days later, showed no evidence of meningitis or other lesions

Microscopic Examination of Exudates and Tissue —Cerebrospinal fluid   In the turbid fluid obtained at the base of the brain approximately 80 per cent of the cells are polymorphonuclear leucocytes and the remainder mononuclear cells   The latter vary in size, many of them having large faintly staining nuclei with abundant protoplasm   Others are typical small mononuclear cells and are not numerous

Meninges   Pieces of tissue including the meningeal exudate and the underlying cortex were removed from the region of the Sylvian fissure, the temporal lobe and the cerebellum, for microscopic examination   The exudate, especially about the blood vessels, is abundant and composed chiefly of polymorphonuclear and mononuclear cells   The relative proportion of these cells varies in different regions   Near the surface of the exudate the polynuclears may comprise 80 per cent or more, while nearer the cortex the mononuclear cells increase in number   Here and there are large endothelial cells, which frequently show phagocytosis of from one to several polynuclear and mononuclear cells   About the blood vessels the exudate is intense, but no changes are observed in the intima or media of the arteries   Thrombi occur in some of the small veins and the thin walls in places are infiltrated with leucocytes   Some free blood is found here and there in the exudate outside the vessels   Very little fibrin is apparent in the formalin-fixed tissue   The cortex shows little change   Occasionally near the surface a polymorphonuclear cell or plasma cell is seen, but deeper no cellular infiltration appears   Changes in the blood vessels and hemorrhages are not present

Peritoneal Fluid   This is slightly turbid and in suspension are a number of leucocytes, 80 per cent of which are small mononuclear, and 20 per cent polymorphonuclear cells   The bacilli are chiefly outside the leucocytes

Intestines   Sections were made of the intestinal wall at different points   In one section the glands of the mucosa show some disintegration and between them are found a few polymorphonuclear cells and eosinophiles   The muscularis is normal and the blood vessels in the subserosa and in the mucosa are engorged   In other sections some congestion and cellular infiltration occur but no changes appear in the serosa

The myocardium, lungs, kidneys, thymus, spleen, adrenals and lymph glands present no noteworthy changes   Sections of the liver show congestion of the small blood vessels and slight infiltration of round cells and leucocytes about some of the bile ducts

GENERAL CONSIDERATIONS

It is unnecessary to review the literature on influenzal meningitis at this time since this has been thoroughly done recently by others Adams,[1] in 1907, tabulated the cases and found 21 in which the influenza bacillus was isolated from the meningeal exudate in pure culture Cohoe[2] this year finds, including his own, 24 cases and gives an analysis of the important features In addition a considerable number of cases are reported in the literature in which a mixed infection of influenza bacilli with, as a rule, Gram-positive diplococci occurred In such cases it is impossible to say how important the influenza bacilli were in causing the lesion It should be stated, however, that in some of these cases the mixed infection was found at autopsy and, as is well known, terminal infection or postmortem invasion with coccus forms is not uncommon, whereas such invasion by influenza bacilli is most unusual It is, therefore, not improbable that most of these cases were primary influenza infections

A sufficient number of cases has now been observed to establish the fact that influential meningitis is a disease of infants and young children and is extremely rare in adults Over one-half the cases reported in the literature occurred in children under one year and the youngest child afflicted was 10 weeks (Fraenkel's first case) The patient whose case is here reported is the youngest on record, being 9 days old at the time of death The infection was probably acquired four or five days previously

According to the clinical report there was little evidence of meningeal trouble, enteritis being the *chief clinical finding noted* The birth was normal The postmortem examination confirmed the intestinal involvement and revealed the presence of a mild peritonitis not recognized macroscopically, and influenza bacilli in pure growth in the peritoneal cavity The question arises in this case as to the possibility of the intestinal lesions being primary and the involvement of the peritoneum and meninges secondary *Cultures of the intestinal contents unfortunately were not made in this case, and, since little or nothing is known about the occurrence of influenza bacilli in the intestinal canal, definite statements can not at present be made In the literature the primary foci are variously given, the lungs, bronchi middle ear and nasal cavities being the sources chiefly suspected Some of the cases are regarded as generalized infections, since multiple abscesses occurred before or fol-

1 Adams   Arch Pediat , 1907, xxiv, 721
2 Cohoe   Am Jour Med Sc , 1909, cxxxvii, 74

lowing the meningeal involvement (Slawyk, Dudgeon, Adams) In a few no statements are made about the primary focus or, as in the piesent case, the poitals of entry usually suspected are entiiely normal A common symptom in these cases, however, is diairhea, and in a considerable numbei a well-marked enteritis has been found at autopsy The intestinal tract apparently has thus far not been suspected as an atiium by any of the writers, notwithstanding the common occurrence of lesions at this point, and, while such an origin may be uncommon, cases like the one here repoited lead one to suspect strongly such a possibility There are no data at hand which will enable one to decide this question definitely, but in the absence of other lesions, especially of the respiiatoiy tract, nasal cavities, middle eai, etc, the intestinal oiigin seems very probable

In few of the cases have extensive bacteriologic studies been made Slawyk[3] obtained the bacilli from the blood, fiom abscesses, meningeal exudate and lungs, others have obtained the bacilli from the spleen In none of the cases have the bacilli been recovered fiom the peritoneal cavity, and peritonitis is not mentioned as a complication in any instance Fisch and Hill[4] report a case of purulent peritonitis from the exudate of which the influenza bacillus was isolated in puie cultuie, but meningeal symptoms did not exist In the present case it is possible that the presence of the influenza bacilli and the slight exudate in the peritoneum resulted from an influenzal bacteriemia, for it is probable that this occurred, notwithstanding the absence of the bacilli in the heait's blood after death Certainly the peritoneal involvement is much more recent than the meningitis and it may be simply a teiminal affair

The general appearance of the brain and meningeal exudate answers very well to the description of influenzal meningitis given by othei writers I may refer particularly to the excellent colored plate illustrating Fraenkel's paper on this subject,[5] which bears a close resemblance to the picture in this present case A striking feature is the greenish-yellow, highly purulent, friable exudate, and, as has been pointed out by Fraenkel, Ghon and otheis, the small amount, or total absence of, fibrin as shown microscopically by special fibrin stains In the formalin-fixed tissue of this case the exudate appears to contain very little fibrin and is made up almost entirely of cells, chiefly of the polymorphonuclear variety In certain places large endothelial cells also are found

3 Slawyk Ztschr f Hyg u Infectionkr, 1899, xxxii, 443
4 Fisch and Hill St Louis Med Review, 1903, xlviii, 19 and 55
5 Fraenkel Ztschr f Hyg u Infectionkr, 1898, xxvii, 315

ingesting other cells A feature distinguishing this form from other forms is the very large number of bacilli in the exudate, both inside and outside the polymorphonuclear cells In meningococcus meningitis the organisms are never so numerous In pneumococcus and streptococcus infections the organisms may occasionally be as numerous, but phagocytosis is either very slight or entirely absent

Changes in the underlying brain substance are limited to a very slight infiltration of leucocytes and plasma cells immediately beneath the pia, while deeper in the tissue and along the blood vessels little or no change occurs This agrees with the findings of others in such cases

Ghon and Fraenkel state that it is not possible to distinguish influenzal meningitis from that produced by the meningococcus or pneumococcus, except by bacteriologic means This is undoubtedly true in many cases The descriptions of influenzal meningitis given in the literature, however, indicate that the exudate as a rule is highly purulent and more copious and wide-spread than that commonly observed in other forms Cellular differentiation of the exudate will not aid, and clinically there is surely no reliable means It may be stated that a highly purulent, massive, meningeal exudate, occurring in an infant or young child, is suggestive of this form, and the influenza bacilli should be sought for by proper methods on hemoglobin media In fact, blood media should be used as a routine in the examination of all meningeal and spinal fluids

A study of the morphological and biological properties of the influenza bacilli isolated in this case reveals no essential differences from those of the bacilli so commonly found in the sputa in various infectious diseases The property of symbiosis is well marked, the small colonies present the typical dewdrop appearance, and are not hemolytic and grow only on hemoglobin media, with a preference for pigeon blood agar The bacilli show only a slight tendency to form threads, are Gram-negative and distinctly bipolar when stained, very susceptible to phagocytosis, and show some pathogenic power for guinea-pigs They agree in every detail with a bacillus received from Dr Wilkinson of Washington, D C, and recovered from the spinal fluid of a non-fatal case of meningitis occurring in a child during convalescence from whooping-cough

The occurrence of a similar condition in the twin brother beginning on the same day, running an almost identical course clinically, and terminating fatally three days after the death of the other child, is worthy of note Unfortunately an autopsy was not made in this case, but the facts strongly suggest a similar infection of common origin in the two cases As already stated, the mother had previously been well and no

membeis of the family were affiieted with "colds" or other diseases Hence the souice of the infection in these cases remains obscure [6]

SUMMARY

Twin brotheis became ill on the fifth day after biith, the cases ian an identical elimical couise and teiminated fatally on the ninth and eleventh days iespectively after birth

There was little oi no distinct clinical evidence of meningeal involvement

Autopsy on the fiist child ievealed as the piominent lesions acute purulent leptomeningitis and acute enteiitis

Fiom the meningeal exudate and fiom the peiitoneal fluid puie cultuies of *B influenzae* weie obtained

The usual atiia of infection—nasal cavity tympanie cavities, lungs, bronehi and throat—weie noimal Omphalitis was not piesent The intestinal tiact is a suspicious portal of entiy

S39 Lakeside Place

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6 Since this aiticle was written Cohen (Ann de l Inst Past, 1909, xxiii, 273) has repoited thiee cases of meningitis in infants caused by an oigamsm belonging to the influenza gioup Moiphologically and cultuially it is identical with Pfeiffei's bacillus but by conglutination tests and ieactivation expeiiments specific diffeiences appear Cohen believes that this oigamsm is the same as that isolated by otheis from cases of meningitis and called *B influenzae* and that the confusion has aiisen because the two oiganisms can be diffeientiated only by specific seium ieactions He calls the infection septicemic cerebiospinal meningitis because a septicemia occuis in the human subject and in moculated animals

THE CLINICAL SIGNIFICANCE OF THE URINARY NITROGEN

III NITROGENOUS METABOLISM IN TYPHOID FEVER

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NEW YORK

The nitrogenous metabolism of typhoid fever has rarely been the subject of systematic study It has long been known that this disease, rather more than other continued fevers, is marked by a very high urinary nitrogen excretion, but the partition of this nitrogen and the bearing of variations in the forms of nitrogenous compounds excreted in the urine on the pathology of the disease has received very scant attention The reason for this paucity of effort lies, not in any supposed lack of importance in the subject, but in the fact that until recently there have been no satisfactory methods for the estimation of the different forms of urinary nitrogen, and no normal standards of comparison Since both of these deficiencies have recently been met and partly removed there would seem to be opportunity for obtaining more significant results than have yet been secured in this field

The total nitrogen excretion in urine and feces in typhoid fever has recently been studied in detail by Benedict and Suranyi [1] The fecal excretion they found comparatively small, forming about 10 per cent of the total nitrogen eliminated During the active febrile period and sometimes continuing into convalescence there is a pronounced loss of nitrogen, excretion exceeding ingestion by as much as 10 grams daily the loss diminishing as the fever subsides Since they were able to limit this loss to some extent by supplying nitrogen-free diet, they argue at length that the excessive nitrogen elimination of typhoid fever is not evidence of toxic destruction of cell proteins but a result of simple hyper activity of metabolic functions They do not discuss the character of the nitrogen partition of the disease, although this consideration would seem to have an important place in the above argument

Von Jaksch and his assistant Erben [2] have furnished the only systematic, but at the same time very meager, data on the partition of the urinary nitrogen in typhoid fever Von Jaksch's first reports [3] he had

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* This article is the third of a series relating to the same general subject References to the former articles are 1 The clinical significance of the urinary nitrogen, Am Jour Med Sc , 1906, cxxxi, 751 2 The metabolism in the toxemia of pregnancy, Am Jour Obst , 1907, lv 289

1 Benedict and Suranyi Ztschr klin Med , 1903, xlviii, 290

2 Erban Ztschr f Heilk , Med Abt , 1904 new series v, 33

3 Von Jaksch Ztschr f klin Med , 1902, xlvii, 1

to recall on account of deficiencies in the methods employed In his second paper[4] he records single complete observations on four febrile cases, each of which showed some increase of amido-acid nitrogen

Erben in 1905 followed one mild case with seventeen examinations over a period of thirty days The highest daily excretion of this patient was 19 6 grams The urea at the height of the fever fell to 74 per cent. of the total nitrogen, but soon rose to 80 per cent plus The courses of both the ammonia and the rest nitrogen described curves with two apices one at the height of the fever, the other three or four days after defervescence This first elevation Erben ascribed rather indefinitely to the febrile process, and the second rise in the rest nitrogen he ventured to refer to resolution of the enlarged lymph nodes It is difficult to find grounds for this latter assumption, or a variant for such deductions from the observation of a single case

The present study was undertaken in 1905 as a control for the interpretation of results obtained by us in the investigation of the urinary nitrogen in the toxemia of pregnancy It was also suggested by an impression which one of us has gathered from many sources that typhoid fever, especially in the later stages of severe and fatal cases, is largely an autointoxication It was thought that the study of the nitrogenous metabolism might indicate to some degree the validity of this conception

That the character of the nitrogen partition might throw light on the nature of some clinical peculiarities of the disease, might control and supplement the present methods of estimating the condition of the patient and determining the diet, might influence the prognosis, or suggest a basis of relapses in the disease, seemed to fall among legitimate expectations The prolonged toxemia of typhoid fever commended itself as a favorable field for observations on some of the less known nitrogenous substances of the urine such as kreatinin, kreatin, and the rest nitrogen Although the results presented are incomplete, especially in respect to fatal cases of the disease, they are not without interest and may have value in several of the relations mentioned

The study was pursued also in the hope of establishing some correlation between changes in the urinary nitrogen and histological alterations in the liver

The fragmentary analyses in Cases 1-11 were made in a preliminary way in 1905, when a few observations in severe and fatal cases were secured through the cooperation of Dr L A Conner For the more complete observations in Cases 12, 13, and 14 we are indebted to our colleague, Dr Philip Shaffer, who carried out the analyses in the summer of 1906. In 1907 we were able to observe several cases in Bellevue

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4 Von Jaksch Ztschr f klin Med , 1903, L 167

Hospital through the courtesy of Dr Alexander Lambert   Our expecta
tions of securing complete observations in severe cases during the sum-
mer of 1908 were partly disappointed, as the disease in New York during
that period proved unusually mild and comparatively rare   Yet three
severe cases were observed in New York Hospital through the active in-
terest of Dr L A Conner

We found it extremely difficult to obtain satisfactory collections of the
twenty-four hour urine from stuporous and incontinent typhoid patients
which were the conditions which it was most desired to observe   In
females especially these difficulties proved almost insurmountable, so that
we would not again attempt such a study in women very sick with ty-
phoid fever   The technical methods employed in this work were those
described in our first contribution on the subject of the "Clinical Sig-
nificance of the Urinary Nitrogen,"[5] and since the general significance
of the urinary nitrogenous substances and their normal variations were
discussed at some length in that article these topics will not be further
considered at this time   It is, however, necessary to point out that a
comparison of normal standards in healthy subjects with the metabolism
of febrile conditions must be undertaken with caution   For example, we
question whether the observations on the influence of starvation in
healthy subjects can safely be transferred to febrile conditions

ANALYSES OF RESULTS

In the analysis of the results the chief interest concerns the relation
of the urinary nitrogen and its partition to the clinical symptoms

TOTAL NITROGEN

The records show a total urinary nitrogen excretion reaching 33 65
gm in an adult weighing 155 pounds, and 29 07 gm in another patient
weighing 148 pounds, but averaging considerably below 20 gm during
febrile periods in all the cases   With the restricted diet of these patients
this large excretion of nitrogen must signify consumption of tissue pro
tein and marked loss of nitrogen on balance   As the diet was uniformly
low in nitrogen consisting of 4 to 6 ounces milk every three hours, or
of similar amounts of meat broth, this factor probably does not dis-
tinctly influence the total nitrogen   Some considerable variations may be
attributable to the activity of the kidneys   There was a general relation
between the weight of the patient and the total nitrogen excreted   Esti
mated according to the weight of the patient the more severe the ty-
phoidal process as judged by the temperature and general condition,

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5 Ewing and Wolf   Am Jour Med Sc 1906 cxxxi 751

the highei the nitiogen output   To this iule, which applies chiefly to the early stages of the disease, theie weie two important exceptions In two cases (19 and 20) toward the end of veiy severe attacks of the disease the total nitiogen was unusually low oi even below normal, 3 to 6 gm, while the febiile pioeess continued   In these cases one has to deal with veiy unusual conditions, such as persistent vomiting, staiva- tion, anemia, and a veiy low state of vitality   In such states one may ieasonably assume that the eneigy evchange is very low, and that after the system has been extensively depleted the febiile typhoid pioeess may continue without the extensive loss of nitiogen which maiks its eailiei stages   In seveial cases (13, 15, 16 and 18) a postfebiile inerease in total nitiogen was observed extending ovei a peiiod of seven days   In two of these cases this inciease was coincident with the addition of two and four eggs to the diet, in a thiid case the amount of meat bioth was eonsiderably inciesed at this time, while in the fourth case (18) no change in the diet was noted   In a fifth case piesenting adequate data (17) no postfebrile inciease oecuiied   We aie theiefoie disposed to iefei this inciease, when it oceuis, to changes in the diet and not, as Eiben has suggested, to resoiption of lymph nodes or any othei essential pioeess in the disease   The postfebiile inciease in iest nitrogen Erben also iefeis to the absoiption of lymph nodes, but in seveial of oui cases such an inerease was clearly explained by the addition of meat to the diet

Whether an antemoitem inciease in nitiogen eveietion oceuis in this disease our observations on fatal cases do not demonstiate, but in Case 9 theie is some indication of such a phenomenon   The highest everetion of nitrogen in propoition to the body weight seems to oceui in the so called toxic cases and peiiods of the disease when the patient appeais poisoned and ean be obseived to be losing weight rapidly   Although these features aie usually coincident with a high tempeiatuie, the total nitrogen seems to be less affected by the fevei than by the intoxieation Thus Patients 18 and 14, weighing 135 and 148 pounds and selected because of the "toxic" chaiactei of the disease, exceited 33 65 gm and 29 07 gm nitrogen, which is relatively much moie than the eveietion in the mildei cases (15, 17 and 16), 14 3, 16 7 and 8 16 gm   In these cases the patients weighed 123, 117 and 67 pounds iespectively, and on the day of these observations had the same temperature, 103° F

UREA

In the majoiity of well-marked cases of typhoid fevei the uiea nitio- gen forms a notably high propoition of the total, even when the patient appeais to be veiy sick   In severe stages it usually runs below 80 pei

cent when 12 to 20 gm of nitrogen are being excreted, while in some cases of recovery it was found below 70 per cent. and even as low as 60 per cent   A ratio below 70 per cent during febrile stages usually indicated a grave condition   The highest ratio, 88 1 per cent, was observed on the twenty-first day of a severe case (14), in which there was a rapid recovery   A review of our results seems to show that a persistently high urea ratio is a favorable sign, yet two fatal cases on first examination gave over 80 per cent urea nitrogen   Sharp increases in this ratio are very favorable signs (Cases 2 and 19), while in two cases (8 and 9) sharp decreases, 82 to 67 per cent and 80 to 60 per cent, in four days, were shortly followed by the death of the patient   In some cases (14, 19, and 22) the urea ratio seemed to be a better index of the patient's condition than were the temperature, pulse, or signs of intoxication

In several cases with rapid convalescence the urea was constantly above 80 per cent, while in two cases with relapses (15 and 17) and in three (16, 19, and 20), with slow convalescence, the urea ratio tended to remain below 80 per cent

Our experience leads us, therefore, to place considerable value on the ratio of urea nitrogen in following the course of typhoid fever, since this ratio very often serves as control on other clinical indications, and may be relied on to a considerable extent to reveal the general type of the disease   The observations on the urea ratio in typhoid fever also seem to lend some support to the view that lesions of the liver established in the course of diseases attended with disturbances of nitrogenous metabolism may have considerable influence on the character of this metabolism   Although we were disappointed in not securing extended observations on fatal cases and no autopsies were obtained we are disposed to assume that the severe degeneration and focal necroses which are nearly constant in the liver of fatal typhoid fever were connected with the sudden decline in the urea-forming function in Cases 8 and 9

During a febrile convalescence somewhat different interpretations of changes in the urea nitrogen ratio seem to be required from those applying to the febrile period   Starvation acidosis or abrupt addition of meat to the diet appeared to be responsible for low urea ratios in Cases 19 and 20

AMMONIA NITROGEN

In one fatal case (9) the ammonia ratio reached 8 9 per cent (2 09 gm)   In one case (15) preceding a relapse, it failed to reach the low level commonly observed   In two very severe cases (19 and 20) during convalescence ammonia nitrogen ratios of 10 per cent and 14 5 per cent

seemed refeiable to slight staivation acidosis At all other times the ammonia ratio was not distinctly above normal, and often it was uniformly low The piesent observations, therefore, do not indicate that acidosis is a piominent feature of typhoid fever Even the highest figures observed indicate only moderate grades of acidosis, especially for patients on a restricted milk diet With a shaip onset of typhoid fevei one would expect to find consideiable acidosis and excess of ammonia from deficiency of food, but none of our cases was observed at the onset of the disease Since acidosis arises from the incomplete burning of fats in the absence of carbohydrates, the relative lack of acidosis in typhoid fever may arise from a pronounced tendency towaid the consumption of proteins rather than fats There are many indications, however, that during fever the complete combustion of fats may be effected without the presence of recently ingested carbohydrates Or the carbohydrate radicles of the proteins may be sufficiently available for the complete combustion of fats In any case, patients suffering from typhoid fever and on practically a starvation diet are comparatively free fiom acidosis Many have insisted that the total ammonia excretion rathei than its ratio to the total urinary nitrogen should be taken as the index of acidosis In many conditions in which the total nitiogen is not high this rule is clearly applicable Yet ammonia possibly has other functions besides that of neutralizing acids, and with every increase in total nitrogen there is normally an increase in absolute ammonia nitrogen In typhoid fever with a daily excretion of 15 to 25 gm nitrogen one can attribute no pathological significance to a modeiate excess ovei the total ammonia excretion of health which has been established by Folin at about 6 7 gm In typhoid fever the total ammonia does not usually much exceed this figure Increased acetone has been found by von Jaksch, and beta-oxybutyric acid by von Noorden The acetone bodies weie not estimated in the present cases

KREATININ

The observations on the excretion of kreatinin and kreatin in typhoid fever seem to have important beaiing not only on the metabolism of this disease but on the general physiological significance of these substances It has been pointed out by Folin[6] that the chief factor determining the elimination of kreatinin is the weight of the person, and he has further defined this factor as the mass of active protoplasmic tissues Shaffer[7] has shown that the hourly excretion of kreatinin is remarkably uniform

6 Folin, O Am Jour Physiol , 1905, viii, 85
7 Shaffer, P Proc Am Soc Biol Chem , 1907, 1, 22 Am Jour Physiol , 1908, xii, 445 Am Jour Physiol , 1908, xxiii, 1

that it is unaffected by great changes in the amount of protein ingested by diuresis, or by active exercise   There is, therefore, a somewhat fixed relation between the kreatinin excreted and the body weight of the subject, which Shaffer expresses as the "kreatinin coefficient," indicating the milligrams of kreatinin nitrogen per kilo of body weight   This coefficient he finds to vary in healthy subjects between 11 7 and 5 4, average 8 4   Very similar coefficients, 8 2 to 7, have been established for dogs by Wolf and Osterberg [8]

Folin suggested that kreatinin excretion is an index of total endogenous or tissue katabolism, but from studies in various pathological conditions, especially in Graves' disease, Shaffer would limit the sources of urinary kreatinin chiefly to the muscles and would interpret the kreatinin coefficient as the expression of muscular and perhaps general cellular efficiency   Similar conclusions were reached by Spriggs,[9] who found low coefficients in cases of muscular dystrophy, amyotonia congenita, and myasthenia gravis   This view is also strongly supported by the observations of Amberg and Morrill [10] who found very low kreatinin coefficients in new-born infants whose muscles are imperfectly developed   A relatively high excretion observed in some fevers Shaffer ascribes to pathological increase in the kreatinin-forming process, coincident with the destruction of body proteins and due to high temperature or the action of bacterial toxins

On the other hand, Mellanby,[11] from an extensive study of the formation and excretion of kreatinin and kreatin, introduces an entirely new point of view in concluding that kreatinin is formed in the liver and is in part converted into kreatin and thus stored in the muscles until the amount of kreatin in the muscles reaches the saturation point, after which the excess of kreatinin continually formed in the liver is excreted in the urine   In cases of hepatic cirrhosis and cancer he found low kreatinin excretion, and in general he is inclined to regard kreatinin excretion as an index of hepatic efficiency

In the present cases the records show that kreatinin excretion is increased during the active periods of typhoid fever and diminishes during convalescence   The total quantity bears a distinct relation to the patient's weight and muscular development   The highest amount observed, 1 06 gm   (K C 15 9), was on the twenty-first day of a severe febrile case (14) in a muscular subject, and the lowest amount seen in

8 Wolf and Osterberg   Biochem Ztschr   1907 v 304
9 Spriggs' Quart Jour Med 1907 i 63
10 Amberg and Morrill   Jour Biol Chem 1907 iii 311
11 Mellanby   Jour Physiol 1908, xxxvi 447

an uncomplicated case, 0 16 gm (K C , 5 7), occuried in a young boy (16) during convalescence In general it may be said that in adults suffering from typhoid fever a kreatinin excretion of over 0 5 gm belongs to the febrile period, while during convalescence the kreatinin nitrogen usually falls below 0 5 gm In one case (20), that of a young girl greatly emaciated and very anemic, it fell to 0 13 gm (K C , 3 6) on the foity-thiid day in convalescence

There is thus distinct evidence of a pathological increase in kreatinin excretion belonging to the typhoid process The highest quantities and the highest coefficients appeai in the seveie stages of the disease while the absolute amounts diminish with convalescence and some very low coefficients appeai in emaciated and very weak subjects (Cases 19 and 20)

These iesults do not enable one to decide between the merits of the contending hypotheses regaiding the significance of kreatinin

During fevei all the piocesses normally involved in nitiogenous metabolism seem to pioceed in increased volume so that the livei, while conceined in elaboiating enoimous amounts of uiea, may also, accoid ing to Spriggs, be pieparing an excess of kieatinin which overflows fiom the muscles to the urine, or, according to Shaffer, the increased muscle metabolism diiectly yields an excess of kieatinin The peculiai muscular weakness which maiks the onset and couise of typhoid fevei veiy probably iesides chieflv in distuibed inneivation, and the high kieatinin excretion at such peiiods may pioperly be inteipieted as of toxic significance The veiy low kieatinin coefficients obseived in some veiy weak and emaciated subjects (as Cases 19 and 20), and the much highei coefficients found in othei patients who withstood the disease moie successfully, favoi Shaffer's hypothesis The piesent data do not seem to offei any new basis for the discussion of the ielation of kieatinin to kieatin

KREATIN

Kreatin appeared in the uiine nearly constantly in the active peiiods of the disease and disappeared during convalescence Its appeaiance is coincident with the peiiod of negative nitiogen balance and general loss of weight The highest amount observed was 1 gm kreatin nitrogen on the sixth day of a severe case (18), when the total nitiogen ieached the highest figure in oui seiies, 33 65 gm , with a nitrogen loss on balance of 30 gm , while the temperature rose to 103 F The patient then weighed 155 pounds and was losing flesh in the iapid manner chaiacteiistic of seveie typhoid fever At this time the kreatin nitrogen was

nearly three times as abundant as the kreatinin nitrogen   Also in Case 20 the kreatin nitrogen several times exceeded the kreatinin nitrogen

The kreatin was rather sensitive to slight disturbances of temperature during convalescence, persisting throughout the slow recovery of Patients 16 and 20 and reappearing with a slight rise of temperature in Case 14 Yet it disappeared before full defervescence in Case 17 and failed to reappear in a mild relapse in Case 15   As a rule the kreatin nitrogen was low in the milder cases and its disappearance from the urine proved a favorable sign

These features are consistent with the view expressed by Shaffer, that kreatin is a product of the destruction of muscle protein

URIC ACID

The uric acid nitrogen varied considerably from day to day, but always within limits that may be regarded as normal   It was highest (maximum 0 46 gm) in the febrile periods and in general exhibited a declining tendency with the fever but failed to show any definite relation to the clinical features   A very low excretion may be noted in one case (15) over a period of four days, during which the temperature was 103° F, while in Case 17 there was some indefinite indication of the postcritical increase reported by Gordes

REST NITROGEN

Changes in the rest nitrogen presented some of the most significant features of the metabolism   Since a fall in urea nitrogen is usually coincident with a rise in rest nitrogen, most of these features have already been indicated in the discussion on urea   During severe febrile periods of favorable cases the urea runs high and the rest nitrogen low but in graver conditions the urea tends to fall below 70 per cent and the rest nitrogen rises toward or above 20 per cent   In two fatal cases (8 and 9) extensive rises in the rest nitrogen to 23 76 per cent and 26 57 per cent (6 24 gm), with corresponding falls in urea, occurred shortly before death   In these fatal cases the urinary sediment contained crystals resembling leucin   We believe, therefore, that the high rest nitrogen of such cases signifies in some degree defective urea forming function of the liver

Since the diet during the severe febrile stages of the disease was very low and uniform an influence on the rest nitrogen from this source may be excluded   During convalescence, however, striking variations in the rest nitrogen seemed clearly referable in several cases, notably in 19 and 20, to the addition of meat to the diet   We interpret this result

as indicating that the organism was at that time unable to metabolize fully the products of digestion of protein food, which therefore passed out in the urine unchanged This observation may be brought in accord with the experiments of Glaessner,[12] who found that feeding amino-acids in certain diseases of the liver was followed by their excretion unchanged in the urine

The significance of high rest nitrogen in the active febrile and in the convalescent afebrile stages of typhoid fever, if our interpretation proves correct, is therefore essentially different In the former period it represents endogenous metabolism, in the latter it may indicate imperfect exogenous or food metabolism It is obvious that this observation may throw light on the significance of the rest nitrogen in many other conditions, and especially in those in which the diet varies For example, a rest nitrogen ratio of 20 per cent, as often observed in moribund cases of acute yellow atrophy in which little or no food has been taken for several days, may have quite a different significance from that of a similar ratio occurring in a case of constipation in an overfed but otherwise healthy subject

While the greater significance of the changes referable to endogenous metabolism may readily be granted, it should be noted that in some of our patients (10 and 16) the addition of meat to the diet, and a consequent rapid rise in rest nitrogen, was marked by a considerable rise in the pulse and temperature and distinct discomfort to the patient Such disturbances in typhoid fever are commonly referred to "indigestion " *"Febris carnis"* is a long-recognized feature of the dietetics of typhoid fever and other diseases It has been variously interpreted, but would seem to receive an adequate explanation in the present urinary analyses

In several cases (12, 14, 15, 16, and 18) we have noted the combination of increased rest nitrogen, increased indicanuria, soon followed by albuminuria

In some instances these features followed the addition of meat or eggs to the diet, while, at the same time, some disturbance of the pulse and subjective condition was commonly observed These attacks, like the former, may probably be interpreted as the result of imperfect metabolism of digested and putrefaction of undigested protein food

Reviewing the data of the foregoing report, perhaps the most notable feature is the demonstration that the severest symptoms of typhoid fever, including high temperature, stupor, and incontinence, may be tolerated with practically a normal urea formation In Case 22 only

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12 Glaessner Ztschr f exper Path u Therap , 1907, iv 336

the high total nitrogen, the kreatinin, and the kreatin would suggest that the patient was not in a normal state of health This patient's tissues, however, were partly protected by the ingestion of considerable food and he made a rapid and complete recovery On the other hand, in fatal cases the nitrogenous metabolism is badly deranged, with a sharp fall in urea nitrogen and corresponding rise in rest nitrogen, showing that in these cases the fatal issue was marked by a collapse in the urea forming function of the organism Between these two extremes fall many cases with varying grades of metabolic disturbance and generally with corresponding departure from the most favorable clinical course

These observations on the integrity of the urea-forming function in severe typhoid fever may be interpreted as favoring the belief of Benedict and Suranyi that the excessive nitrogen elimination of typhoid fever is not evidence of toxic destruction of cell proteins but a result of simple hyperactivity of metabolic functions Yet these patients are often extremely ill, they present the clinical signs of intoxication, including stupor, subsultus, and rapid emaciation, and, unless one chooses to call nothing toxic which is not abnormal in type, the very activity of the nitrogenous metabolism in typhoid fever must be included as a factor in the morbid complex of the disease That this hyperactivity is not directly connected with the neutralization of typhoid endotoxins may readily be granted without lessening its importance as a source of morbid phenomena in the disease Moreover, the excessive urea formation is associated with high excretion of kreatin and kreatinin which are distinctly abnormal features of metabolism

Since in the so-called fatal toxic cases this hyperactivity of the urea-forming function is not maintained, one must conclude that death in these cases is partly referable to a loss of efficiency in these overacting functions If this conclusion is correct it offers support to the view that fatal uncomplicated typhoid fever is largely an auto-intoxication, in all the essential particulars in which that condition is now understood

A second fact of special interest in these data is the different significance which seems to belong to the rest nitrogen in severe febrile stages of the disease in patients taking little or no protein food, from that attaching to the rest nitrogen in convalescent cases when protein food is first added to the diet In the former condition a high rest nitrogen would seem to indicate that the endogenous metabolism is faulty and that the organism fails to synthesize urea even from its own native ingredients Under these conditions a high rest nitrogen indicates a grave defect in metabolic functions In convalescence however when the endogenous metabolism is practically normal the organism is un-

able properly to metabolize ingested alien amino-acids which pass out in the urine unchanged   Here the resulting high rest nitrogen is of much less serious significance, although sometimes attended with subjective disturbances

These observations on the occurrence of high rest nitrogen in two periods of typhoid fever seem to us to support the view that the anatomical alterations in the liver of typhoid fever are essentially connected with the disturbance of metabolism   They also suggest caution in the early addition of meat to the diet of convalescent typhoid patients

In several cases, notably on the thirty-eighth day in Case 16, the simultaneous occurrence of increased rest nitrogen, indicanuria, and albuminuria was noted and often subjective symptoms were added, such as fever, acceleration of pulse, vomiting, and general discomfort   The increased rest nitrogen in these cases we interpret as the result of defective function of the liver and failure to change amino-acids into urea

An excessive formation of indol from intestinal putrefaction, may be a factor in the disturbance by interfering with the nutrition of this organ   These observations, which we have duplicated in the toxemia of pregnancy seem to explain the *febris carnis* and may be of significance in the etiology of nephritis and in the relation of disturbances of the liver to Bright's disease   Whether attacks of this character have any relation to relapses in the disease has not been demonstrated in these data, but it would seem not improbable that disturbances in metabolism may have important influence in this direction

Finally, the most obvious conclusion of this study is the inadequacy of the diet used in these cases and of that generally employed in typhoid fever   When a patient is losing 20 to 30 gm of nitrogen daily on balance it can not be said that any success is being attained in combating the most important feature of the metabolic disturbance in the disease

REPORTS OF CASES

CASE 14 —*Patient*—Muscular negro, aged 26, normal weight, about 165 or 170 pounds, admitted to Bellevue Hospital March 19, 1907, service of Dr Alex ander Lambert   He had lost considerable flesh before admission and on the twenty-second day weighed 148 pounds   on the thirty-second day, 139 pounds, on the thirty-eighth day, 148 pounds   Blood examination on the seventeenth day gave 5,600 leucocytes 50 per cent polynuclear, Widal reaction positive and culture positive   The patient presented the appearance of a rather toxic type of the disease   He emaciated rapidly and the mental condition was somewhat stuporous, although the temperature was not high   These features coincide with the high nitrogen output   The nitrogen partition, however, was normal the urea ratio being one of the highest observed in this series of cases, and this fact we are disposed to connect with the rapid and complete recovery and the freedom from com-

plications The case suggests a dependence of the toxic condition on the excessive protein destruction, and raises the question whether these toxic features might not have been reduced if the protein destruction could have been prevented

Diet —On the ninth and tenth days the patient received 2 8 gm N, 75 calories, in the form of chicken broth and gelatin, and excreted 23 5 and 28 7 gm N, a total loss of 46 6 gm in the two days On the following five days he received 2 9 gm N, 171 calories, and excreted 29 to 21 gm N On the twenty eighth day the diet was raised to 311 calories with 3 9 gm N Thereafter there was a steady fall in nitrogen excretion, except on the thirty third day, when 27 2 gm were

TABLE 1 —URINARY ANALYSIS, CASES 1 TO 11 *

Case No	Day of Disease	Volume c c	Total Nitrogen Gm	Urea N %	Ammonia N %	Rest N %	Albumin	Temp	General Condition
1	21	1100	16 72	64 2	2 9	15 21	++	104 2	
	22	740	11 94	77	2 8	13 1	++	101	Brighter
2	26	865	15 78	73 4	4 34	18 82	O	102 5	Restless
	30	1210	17 67	85 5	1 89	9 43	O	103 5	Comfortable
3	26	1135	7 12	78 9	4 1	11 6	O	99	Comfortable
	28	1200	6 6	78 7	7 7	8 9	+	99 2	
4	7	460		78 0	5 63	15 7	++	108 5	Acute nephritis
5	24	325		75 7	2 21	20 6	+	102 5	Died 25th day
6	16	365		66 4	6 68	22 9	+	102	Serious
7	14	960	12 20	69 5	1 96	9 85	+	104	Delirious
	16	1100	13 33	66 8	2 17	11 3	+	104	Delirious
8	33	760	7 80	81 9	3 4	9 69	+	100	Delirious Inconti nent
	37	330		67 0	6 12	23 76	+	100 5	Died 41st day
9	26	760	18 4	80 13	7 91	7 82	+	105	Incontinent Dull
	30	1330	23 5	60 27	8 9	26 57	+	105	Stupor, Died 32d day
10	35	990	19 2	74 9	5 81	13 4	+	104	Fair
	41	500	10 2	72 5	6 47	13 5	+	103 5	Fair
11	10	1400	15 7	77 2	5 29	14 12	+	104 5	Fair
	25	460		80 3	3 45	14 9	+	105 5	Relapse

* In these cases the rest N was determined directly by the Pfaundler method

eliminated The heat value and nitrogen content of the food were also raised on the thirty-third day to 5 5 gm N and 798 calories, on the thirty-fifth day to 6 8 gm N and 1 360 calories, on the thirty seventh day to 9 0 gm N and 1 845 calories

CASE 15 —*Patient* —Man, aged 26 admitted to Bellevue Hospital March 24, 1907, service of Dr Alexander Lambert, weight, eighteenth day, 123 pounds, thirty second day 109 pounds, thirty seventh day, 115 pounds, forty third day, 119 pounds On the twentieth to twenty third days the patient was dull by day, restless at night and complained of abdominal pain diarrhea, epistaxis, anorexia, from the twenty-fourth day comfortable Blood examination gave 9 500 leucocytes,

60 per cent polynuclear Widal incomplete, culture positive The relapse about the forty-fourth day was associated with pharyngitis and indicanuria, but without typhoidal symptoms

TABLE 2—Urinary Analyses, Case 12

Volume	Total Nitrogen	Urea N		NH₃ N		Kreatinin N		Uric Acid N		Rest N		Albumin	Temp	General Condition
	Gm	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%		99	
760	10 03	8 01	79 8	0 90	8 9	0193	1 9	15	1 4	78	8 0	O	102 5 / 100	Comfortable
1300	18 67	14 9	80 2	1 00	5 4	47	2 5	29	1 6	19	10 3	O	102 / 101 5	Comfortable
1135	18 20	14 2	77 9	1 16	6 4	43	2 3	27	1 5	22	11 9	O	98 6 / 100 2	Comfortable
1470	16 40	13 5	82 8	1 04	6 4	37	2 3	26	1 6	12	7 2	O	99 / 100 2	Comfortable
1510	26 80	20 2	75 3	1 66	6 2	64	2 4	42	1 6	39	14 5	O	98 6 / 99	Comfortable
670	9 35	7 56	80 9	0 46	4 9	24	2 6	16	1 7	93	9 9	+	98 6 / 99	Comfortable
970	10 30	8 20	79 4	0 59	5 7	25	2 4	13	1 2	1 14	11 0	+	101 / 101	Headache
													104	Relapse

TABLE 3—Urinary Analysis, Case 13

Disease	Volume	Total Nitrogen	Urea N		NH₃ N		Kreatinin N		Uric Acid N		Rest N		Albumin	Temp	General Condition
		Gm	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%		102	
3	1475	27 40	23 3	85 0	1 61	5 9			32	1 2	22	7 9	O	99 5 / 100	Fairly Good
4	665	12 47	10 1	81 1	0 70	5 6	36	2 9	19	1 5	11	8 9	O	99 2 / 99 6	Good
5	325?	5 95	4 88	8 27	0 29	4 8	16	2 7	08	1 3	0 5	8 5	O	98 6 / 99 8	Good
7	985	10 90	9 14	84 0	0 55	5 0	30	2 9	17	1 6	0 7	6 5	O	98 6 / 99 6	Good
8	1080	12 25	10 5	87 0	0 51	4 1	33	2 7	18	1 5	58	4 7	O	98 6 / 99	Good
1	2075	16 45	14 7	85 7	0 74	4 5	42	2 5	15	0 9	1 38	8 4	O	98 6 / 99 4	Good
3	2225	19 20	16 6	86 6	0 85	4 4	49	2 5	19	1 0	11	5 5	O	98 6 / 99 8	Good
8	1900	20 95	18 5	88 2	0 95	4 5	47	2 2	19	09	0 9	4 2	O	98 4	Good

This case represents a sharp attack of typhoid fever rapidly improving The chief point of interest is the rapid change in the nitrogen partition coincident with improvement in the clinical status The considerable loss of weight and the rather low urea N seem to coincide as features of a somewhat severe typhoidal process

Diet—From the fourth to eighth days the patient received chicken broth, jelly and crackers, total N content, 3 60 gm During this time the N elimination varied between 13 and 14 gm , a loss per day of about 10 0 gm On the sixteenth day eggs and rice were given, increasing the nitrogen ingested to 5 51 gm and

TABLE 4—URINARY ANALYSES, CASE 14

Day of Disease	Volume c c	Sp Gr	React	Albumin	Indican	T—N Gm	Gross Urea N Gm	Gross Urea N %	NH₃ N Gm	NH₃ N %	Urea N Gm	Urea N %	Kreatinin N Gm	Kreatinin N %	Kreatin N Gm	Kreatin N %	Uric Acid N Gm	Uric Acid N %	Rest N Gm	Rest N %	Kreatinin Coefficient	Temp
21	1930	1021	acid	+	+	23.54	21.52	91.4	0.78	3.3	20.74	88.1	0.76	3.2	0.11	0.4	0.23	1.0	0.92	4.0	11.3	102.4
22	1710	1022	acid	+	+	28.7	25.40	88.5	1.01	3.5	24.39	85.0	1.06	3.7	0.00	0.0	0.23	0.8	2.01	7.0	15.9	102.8
23	1700	1021	acid	+	0	29.07	24.14	83.0	0.82	2.8	23.32	80.2	0.83	2.8	0.26	0.9	0.32	1.1	3.52	12.2	12.5	103
24	1300	1022	acid	+	0	22.50	19.02	84.5	0.78	3.5	18.24	81.0	0.46	2.0	0.53	2.4	0.30	1.3	2.19	9.8	6.9	102
25	1600	1021	acid	+	0	28.65	24.50	85.5	0.88	3.1	23.62	82.4	0.98	3.4	0.30	1.0	0.37	1.3	2.50	8.8	14.7	101
26	1300	1021	acid	+	0	21.05	18.20	86.4	0.68	3.2	17.52	83.2	0.68	3.2	0.51	2.4	0.27	1.3	1.39	6.7	10.2	100.5
27	1310	1020	acid	0	+	20.90	17.89	85.6	0.25	1.2	17.64	84.4	0.80	3.8	0.59	2.8	0.10	0.5	1.52	7.3	12.0	100
28	1710	1020	acid	+	0	23.10	19.83	85.9	0.65	2.8	19.18	83.1	0.95	4.1	0.51	2.2	0.22	0.9	1.50	6.9	14.3	100.2
29	1090	1023	acid	+	0	18.25	15.51	85.0	0.23	1.3	15.28	83.7	0.81	4.4	0.20	1.1	0.19	1.0	1.54	8.5	12.2	99.2
30	1570	1017	acid	+	0	18.70	15.95	86.2	0.63	3.4	15.32	82.8	0.82	4.4	0.11	0.6	0.22	1.2	1.40	7.6	12.3	98
31	1190	1016	acid	+	0	16.80	14.23	84.7	0.57	3.4	13.66	81.3	0.76	4.5	0.18	1.1	0.22	1.3	1.41	8.4	11.4	99
32	1400	1014	acid	0	+	15.04	12.86	85.5	0.59	3.9	12.27	81.6	0.74	4.9	0.08	0.5	0.21	1.4	1.15	7.7	11.8	99
33	1100	1010	acid	0	++	27.97	25.94	93.5	0.42	1.5	25.52	92.0	0.67	2.4	0.04	0.2	0.15	0.5	0.97	3.4	10.6	98
34	1780	1008	acid	0	0	13.61	11.31	83.6	0.76	5.6	10.58	78.0	0.76	5.6	0.00	0.0	0.23	1.7	1.28	9.1	12.1	99
35	2710	1008	acid	0	0	13.02	10.90	83.7	0.66	5.1	10.24	78.6	0.79	6.1	0.00	0.0	0.22	1.7	1.11	8.5	12.6	99
36	2170	1007	acid	+	0	12.74	10.74	84.3	0.70	5.5	10.04	78.8	0.70	5.5	0.00	0.0	0.32	2.5	0.98	7.7	11.1	99.2
37	2490	1007	acid	++	++	11.21	8.74	78.0	0.72	6.4	8.02	71.6	0.85	3.3	0.17	1.5	0.08	0.7	1.85	16.5	5.9	99
38	2860	1007	acid	+	++	12.74	10.90	86.9	0.60	4.8	10.30	82.1	0.27	2.9	0.23	1.8	0.20	1.6	0.84	6.9	5.9	100.5

TABLE 5.—URINARY ANALYSES, CASE 15

Day of Disease	Volume c.c.	Sp Gr	Reaction	Albumin	Indican	Total N Gm	Gross Urea N Gm	Gross Urea N %	NH₃ N Gm	NH₃ N %	Urea N Gm	Urea N %	Kreatinin N Gm	Kreatinin N %	Kreatin N Gm	Kreatin N %	Uric Acid N Gm	Uric Acid N %	Rest N Gm	Rest N %	Kreatinin Coefficient	Temp
5	730	1023	acid	+	O	14 30	10 56	73 8	0 94	6 6	9 62	67 2	0 42	29	0 00	00	0 28	20	3 04	213	68	103 5
6	760	1021	acid	+	+	14 61	12 22	83 6	1 32	9 0	10 90	71 6	0 55	38	0 28	19	0 05	04	1 51	103	90	103
7	660	1020	acid	+	++	13 26	10 90	82 2	1 11	8 4	9 79	73 8	0 48	36	0 15	11	0 06	08	1 67	123	78	103
8	640	1023	acid	++	+	13 07	10 53	80 6	0 91	7 0	9 62	73 6	0 56	43	0 10	08	0 01	01	1 87	142	91	103 4
9	810	1022	acid	++	+	15 65	12 70	81 1	1 17	7 5	11 53	73 6	0 60	38	0 32	20	0 02	01	2 01	130	98	102 2
10	930	1021	acid	+	O	17 26	14 22	82 4	1 18	6 8	13 04	75 6	0 56	32	0 28	16	0 30	17	1 90	111	91	103
11	1390	1014	acid	+	+	15 03	12 51	83 2	1 49	9 9	11 02	73 3	0 71	47	0 07	05	0 27	18	1 47	98	116	102 5
12	2060	1009	acid	+	O	12 97	10 73	82 7	1 24	9 6	9 49	73 1	0 62	48	0 10	08	0 27	21	1 25	96	101	102 6
13	1780	1013	acid	O	+	12 28	9 96	81 1	1 00	8 1	8 96	73 0	0 52	42	0 18	15	0 28	23	1 34	109	85	102
14	1200	1016	alk	+	++	10 72	8 17	76 2	0 62	5 8	7 55	70 4	0 36	34	0 22	21	0 17	16	1 80	167	59	99 4
15	2370	1008	alk	O	+++	10 73	8 79	81 9	0 92	8 6	7 87	73 3	0 36	34	0 31	29	0 21	20	1 06	98	59	100 2
16	1770	1011	acid	O	+++	12 41	10 11	81 5	0 62	5 0	9 49	76 5	0 44	35	0 30	24	0 30	24	1 26	102	72	98 4
17	2870	1007	acid	O	++	11 48	9 76	85 0	0 80	7 0	8 96	78 0	0 46	40	0 00	00	0 23	20	1 03	90	74	98 2
18	2650	1007	acid	O	+	10 58	8 89	84 0	0 53	5 0	8 36	79 0	0 48	45	0 00	00	0 24	23	0 97	92	78	99
19	3125	1007	acid	O	++	14 34	11 74	81 9	0 62	4 3	11 12	77 6	0 47	33	0 00	00	0 25	17	1 88	131	77	98
20	2855	1007	acid	O	+	11 78	10 37	88 0	0 57	4 8	9 80	83 2	0 43	36	0 00	00	0 20	17	0 78	67	72	98
29	1925	1008 Relapse	acid	O	++	8 37	7 62	91 1	0 52	6 2	7 10	84 9	0 27	32	0 00	00	0 08	10	0 40	47	44	101 2
30	3020	1007	acid	O	+++	12 53	11 18	89 2	0 85	6 8	10 33	82 4	0 57	45	0 00	00	0 27	22	0 51	41	93	100
31	3300	1004	acid	O	+	8 25	7 03	85 2	0 63	7 6	6 40	77 6	0 10	48	0 00	00	0 17	21	0 65	79	65	99
32	3320	1004	alk	O	+	8 36	7 50	89 7	0 73	8 7	6 77	81 0	0 46	55	0 00	00	0 20	24	0 20	24	75	99
33	4490	1003	alk	O	+	9 02	8 08	89 6	2 07	230 ?	6 01	66 6	0 49	54	0 00	00	0 22	24	0 23	26	80	98

TABLE 6 — URINARY ANALYSIS, CASE 16

Day of Disease	Volume cc	Sp Gr	Reaction	Albumin	Indic in	Total N Gm	Gross Urea N Gm	Gross Urea N %	NH3 N Gm	NH3 N %	Urea N Gm	Urea N %	Kreatinin N Gm	Kreatinin N %	Kreatin N Gm	Kreatin N %	Uric Acid N Gm	Uric Acid N %	Rest N Gm	Rest N %	Weight, Kilos	Kreatinin Coefficient	Temp
17	850	1015	acid	0	+	8.16	6.65	81.5	0.33	4.0	6.32	77.5	0.30	3.7	0.11	1.3	0.21	2.6	0.89	10.9	30.6	9.8	103.2
18	1010	1015	acid	+	+	7.70	6.28	80.6	0.56	7.2	5.72	74.4	0.28	3.6	0.02	0.3	0.15	1.9	1.06	13.6		9.1	103.2
19	1000	1016	neutr	0	0	7.71	6.68	86.6	0.48	6.2	6.20	80.4	0.24	3.1	0.13	1.7	0.13	1.7	0.53	6.9		7.8	101.4
20	1800	1009	acid	0	++	9.85	8.07	81.9	0.39	4.0	7.68	77.9	0.26	2.6	0.28	2.8	0.22	2.2	1.02	10.5		8.5	102.2
21	850	1020	acid	0	0	11.08	9.25	83.5	0.59	5.3	8.66	78.2	0.23	2.1	0.36	3.2	0.23	2.1	1.01	9.1		7.5	102
22	1665	1008	acid	0	+	7.97	6.41	80.4	0.50	6.3	5.91	74.1	0.23	2.9	0.07	0.9	0.17	2.1	1.09	13.7		7.5	101
23	1100	1013	acid	+	+++	8.70	6.70	78.8	0.52	6.1	6.18	72.7	0.23	3.2	0.24	2.9	0.20	2.4	1.10	12.7		8.5	100
24	1105	1010	acid	+	+++	7.91	6.45	81.5	0.43	5.4	6.02	76.1	0.18	2.3	0.13	1.6	0.20	2.5	0.95	12.1		5.9	100.5
25	1175	1010	acid	+	+	8.47	6.85	81.8	0.65	7.8	6.20	74.0	0.29	3.5	0.13	1.6	0.23	2.7	0.87	10.4		9.4	101
26	1005	1013	acid	0	+	6.65	5.44	82.1	0.44	6.6	5.00	75.5	0.18	2.7	0.14	2.1	0.18	2.7	0.69	10.4	27.2	5.9	100
27	1000	1009	alk	0	++	7.06	5.90	83.6	0.66	9.4	5.24	74.2	0.26	3.7	0.12	1.4	0.17	2.4	0.61	8.9		8.5	101
28	1100	1013	amph	0	+	10.82	9.06	83.7	0.47	4.3	8.59	79.4	0.38	3.5	0.00	0.0	0.28	2.6	1.10	10.2		12.3	99.5
29	1615	1010	alk	0	+	7.60	6.17	81.2	0.49	6.4	5.68	74.8	0.28	3.7	0.07	0.9	0.18	2.4	0.90	11.8		9.6	98
30	1565	1009	alk	+	+	6.84	5.47	80.0	0.36	5.3	5.11	74.7	0.25	3.7	0.00	0.0	0.14	2.0	0.98	14.3		9.1	100
31	1270	1009	alk	+	0	7.77	6.04	83.3	0.39	7.0	4.25	76.3	0.25	4.5	0.00	0.0	0.13	2.3	0.55	9.6		9.1	99
32	1710	1009	alk	0	0	7.70	6.16	82.1	0.72	6.9	5.64	75.2	0.31	4.1	0.00	0.0	0.19	2.5	0.84	11.3		11.4	99.6

No.																							
33	1765	alk	1008	o	+	815	707	839	053	63	656	776	035	11	000	00	022	26	079	94		128	99 4
34	1325	alk	1009	o	+	604	505	836	038	63	467	773	027	15	000	00	011	23	058	96		99	100
35	1225	alk	1012	o	+	621	526	847	040	76	479	771	027	13	000	00	017	27	051	83		99	100
37	1040	acid	1015	+	+++	884	832	911	052	59	780	882	019	22	000	00	009	10	024	27		69	103
38	1330	acid	1012	+	++	706	597	846	039	55	578	791	028	10	000	00	013	18	068	96		102	101
39	745	acid	1012	o	+++	600	378	630	022	36	356	594	019	32	013	22	016	27	174	289		69	102
40	1145	alk	1011	+	+	529	358	677	029	57	329	622	021	13	007	13	011	27	127	240	278	82	1015
41	2025	acid	1008	o	+	745	640	859	077	103	563	736	032	13	000	00	016	22	057	76		115	100
42	1320	acid	1009	+	+	560	475	818	015	80	430	768	026	16	000	00	014	23	045	81		93	100
43	1410	alk	1010	o	+	517	416	863	027	52	419	811	027	52	000	00	011	21	033	64	272	99	1005
44	1340	alk	1008	o	+	537	406	756	040	74	366	682	021	39	000	00	012	22	098	183		77	101
45	1600	alk	1009	o	+	632	560	886	054	87	506	801	022	35	000	00	013	21	037	58	280	78	1005
46	1690	alk	1010	o	+	676	592	876	051	77	541	801	026	38	000	00	015	22	043	64		92	100
47	1240	alk	1009	o	+	485	426	878	012	89	383	789	021	11	000	00	012	25	026	53		75	100
48	1580	alk	1008	o	+	600	526	877	039	65	487	812	024	10	000	00	011	23	036	60		85	995
49	1660	acid	1009	o	+	674	573	876	073	81	720	795	023	35	005	08	013	20	040	61		82	992
50	1420	acid	1011	o	+	713	619	868	060	81	759	784	028	39	004	06	011	20	048	67		100	994
51	1375	acid	1010	o	+	580	511	881	022	38	489	813	019	33	003	05	011	19	036	67		67	
52	745	acid	1013	o	+++	559	481	860	039	70	442	790	016	29	002	04	013	23	047	84		57	
53	1420	acid	1007	o	++	673	582	891	038	75	411	833	019	29	001	06	010	15	038	59		67	
54	1770	acid	1008	o	o	538	471	877	053	96	419	757	023	13	004	07	009	17	031	58	314	73	

the heat value to 456 calories There was no marked change in the nitrogen content of the urine On the twentieth day the patient received 7 06 gm N and 1,034 calories The nitrogen output was still 11 78 gm

CASE 16 —*Patient*—Male, aged 13, admitted to Bellevue Hospital, April 2, 1907, service of Dr Alexander Lambert During the seventeenth to twentieth days of the disease the patient was restless, on the twenty-first day comfortable, on the twenty-second day hungry On the seventeenth day the blood gave a positive Widal reaction, and showed 5,000 leucocytes, of which 64 per cent were polynuclear The weight ran as follows Seventeenth day, 67 pounds, thirtieth day, 60 pounds, thirty-ninth day, 62 pounds, forty-second day, 60 pounds, forty-fourth day, 64 pounds, fifty third day, 70 pounds

This case is one of a mild typhoid fever in a young boy On the thirty sixth day of the disease there was a mild relapse lasting about one week It was attended by marked albuminuria and indicanuria The total nitrogen rose slightly, the urea N fell from 88 per cent to 59 per cent, kreatin reappeared, uric acid increased, and the rest N rose from 2 7 per cent to 28 9 per cent

Diet—From the seventeenth to twenty-sixth days the patient received chicken broth, crackers and jelly, containing 3 0 gm N and 218 calories During this period there was a daily loss of N of about 4 gm From the twenty-seventh to thirty-seventh days he received 5 5 gm N and 789 calories The nitrogen excretion then varied between 6 and 10 gm Toward the end of the observations he received 6 8 gm N and about 1,774 calories, while the nitrogen output ran between 5 and 7 gm Before leaving the hospital he was placed on soft diet, of which the nitrogen and calorie value were not determined

CASE 17 —*Patient*—Man, aged 29, admitted to Bellevue Hospital April 3, 1907, service of Dr Alexander Lambert Weight, eleventh day, 117 pounds, thirty sixth day, 112 pounds The patient was at no time very sick, complaining chiefly of headache and neuralgic pains Blood examination on the eventh day showed 6,800 leucocytes, Widal positive, culture positive The chief point of interest is the slight change in the nitrogen metabolism and the mild symptoms Nevertheless there was a mild relapse covering the forty third to fifty-sixth days

Diet—From the twelfth to the twenty third days of the disease the patient received a diet of crackers, jelly and chicken broth, containing 3 2 gm N and 219 calories From the twenty-third to thirtieth days rice was added, making 4 94 gm N and 640 calories The output at this time was 10 8 to 14 gm N

CASE 18 —*Patient*—Man, aged 29, weight 155 pounds, admitted to Bellevue Hospital April 8, 1907, service of Dr Alexander Lambert On the sixth day patient complained of severe headache, difficult urination, and took very little food Definite improvement began on the eighth day

This case presents the termination of a rather severe attack of typhoid fever The chief point of interest is the high total nitrogen of the sixth day, with normal partition In the third week sharp increases in the rest nitrogen were associated with increasing albuminuria and high indicanuria

Diet—From the sixth to eleventh days he received arrowroot jelly, rice, butter and chicken broth, containing 2 8 gm N and 1,671 calories, including 720 calories in butter On the seventh day he eliminated 33 6 gm N a net loss for that day of 30 gm, equal to 900 gm of muscle tissue During the rest of this period he excreted in the urine 16 to 20 gm N daily From the fourteenth to twenty-third days he was given hominy and chicken broth, containing 2 5 gm N and 425 calories The nitrogen output during this period fell to 8 6 gm

CASE 19 —*Patient*—Woman, aged 35 Illness began acutely six days before admission to New York Hospital, service of Dr Conner, Aug 12, 1908 The patient ran through a very severe attack of typhoid fever, the temperature reaching 104 F or above from the seventh to eighteenth day, declining abruptly on the twenty-first day During the febrile period there were constant delirium or

TABLE 7—URINARY ANALYSES, CASE 17

Day of Disease	Volume c.c.	Sp Gr	Reaction	Albumin	Indican	Total N Gm	Gross Urea N Gm	Gross Urea N %	NH₃ N Gm	NH₃ N %	Urea N Gm	Urea N %	Kreatinin N Gm	Kreatinin N %	Kreatin N Gm	Kreatin N %	Uric Acid N Gm	Uric Acid N %	Rest N Gm	Rest N %	Temp
12	890	1025	acid	+	++	16 68	14 31	85 8	0 61	3 7	13 70	82 1	0 75	4 5	0 25	1 5	0 28	1 7	1 09	6 5	103 2
13	890	1024	acid	+	+	13 79	12 03	87 2	0 52	3 8	11 51	83 4	0 38	2 8	0 11	0 8	0 18	1 3	1 09	7 9	103 2
14	1420	1017	acid	+	+	16 75	14 06	83 9	0 40	2 4	13 66	81 5	0 64	3 8	0 11	0 7	0 34	2 0	1 60	9 6	103 2
15	1600	1015	acid	0	0	16 27	13 76	84 6	0 80	4 9	12 96	79 7	0 61	3 7	0 18	1 1	0 30	1 8	1 42	8 8	103 4
16	1670	1013	acid	+	+	14 35	12 06	84 0	0 68	4 8	11 38	79 2	0 43	3 0	0 27	1 9	0 28	2 0	1 31	9 1	103 2
17	1350	1017	acid	0	+	17 15	14 68	85 6	0 71	4 1	13 97	81 5	0 61	3 6	0 15	0.9	0 36	2 1	1 35	7 8	103
18	1245	1015	acid	+	+	12 82	10 46	81 6	0 51	4 0	9 95	77 6	0 17	1 3	0 23	1 9	0 26	2 0	1 70	13 2	103 6
19	1665	1013	acid	+	+	14 45	12 23	84 6	0 65	4 5	11 58	80 1	0 43	3 0	0 13	0 9	0 33	2 3	1 33	9 2	102 2
20	1285	1018	acid	+	+	16 35	13 78	84 3	0 76	4 6	13 02	79 7	0 53	3 0	0 23	1 4	0 39	2 4	1 42	8 7	102
21	1920	1013	acid	+	+	15 38	13 40	87 1	0 63	4 1	12 77	83 0	0 54	3 5	0 15	1 0	0 32	2 1	0 97	6 3	101 4
22	1620	1013	acid	+	+	14 31	12 40	86 7	0 68	4 8	11 72	81 9	0 47	3 3	0 00	0 0	0 29	2 0	1 15	8 0	102
23	1915	1012	acid	+	0	14 61	12 20	83 5	0 75	5 1	11 45	78 4	0 50	3 4	0 00	0 0	0 31	2 1	1 60	11 0	100
24	2035	1011	acid	+	+	14 01	11 97	85 4	0 77	5 5	11 20	79 9	0 47	3 4	0 00	0 0	0 26	1 9	1 31	9 3	102
25	2030	1011	acid	+	+	12 98	10 74	82 7	0 77	5 9	9 97	76 8	0 49	3 8	0 00	0 0	0 28	2 2	1 47	11 3	101 2
26	2500	1008	acid	+	0	12 67	10 80	85 2	0 75	5 9	10 05	79 3	0 50	3 9	0 00	0 0	0 30	2 4	1 07	8 5	99 6
27	1745	1010	acid	+	+	11 13	9 47	85 1	0 66	5 9	8 81	79 2	0 40	3 6	0 00	0 0	0 28	2 5	0 98	8 8	101 2
28	1755	1011	acid	+	+	11 28	9 28	82 3	0 68	6 0	8 60	76 3	0 42	3 7	0 00	0 0	0 30	2 7	1 28	11 3	101 2
29	2220	1008	acid	+	+	10 79	9 35	86 6	0 84	7 8	8 51	78 8	0 44	4 1	0 00	0 0	0 27	2 5	0 73	6 8	100
30	1805	1012	alk	0	0	10 81	8 97	83 0	0 74	6 8	8 23	76 2	0 47	4 3	0 00	0 0	0 27	2 5	1 10	10 2	100
31	3525	1008	acid	0	+	11 98	10 00	83 5	0 99	8 3	9 01	75 3	0 56	4 7	0 00	0 0	0 35	2 9	1 07	8 9	100
32	2270	1008	acid	+	+	10 98	9 53	86 8	0 39	3 5	9 14	83 3	0 11	3 7	0 00	0 0	0 36	3 3	0 66	6 2	98 4

TABLE 8 — URINARY ANALYSIS, CASE 18

Day of Disease	Volume C.C.	Sp Gr	Reaction	Albumin	Indican	Total N Gm	Albumin N Gm	Gross Urea N Gm	Gross Urea N %	NH₃ N Gm	NH₃ N %	Urea N Gm	Urea N %	Kreatinin N Gm	Kreatinin N %	Kreatin N Gm	Kreatin N %	Uric Acid N Gm	Uric Acid N %	Rest N Gm	Rest N %	Temp
6	1531	1023	acid	++	+	33.65		28.80	85.6	0.80	2.4	28.00	83.2	0.38	1.1	1.00	3.0	0.46	1.4	3.01	8.9	103
7	975	1021	acid	++	+++	19.35		15.90	82.2	0.68	3.5	15.22	78.7	0.58	3.0	0.16	0.8	0.31	1.6	2.40	12.4	103.4
8	1165	1021	acid	++	+	20.29		17.41	85.8	0.59	2.9	16.82	82.9	0.65	3.2	0.42	2.1	0.43	2.1	1.38	6.8	103
9	1160	1017	acid	+	++	16.95		14.41	85.0	1.06	6.3	13.35	78.7	0.68	4.0	0.00	0.0	0.35	2.1	1.51	8.9	102.4
10	810	1020	acid	+	+	14.05		11.80	84.0	0.59	4.2	11.21	79.8	0.15	1.1	0.23	1.6	0.31	2.2	1.56	11.1	103
11	925	1020	acid	+	+	16.50		14.00	84.8	0.65	3.9	13.35	80.9	0.57	3.5	0.13	0.8	0.42	2.5	1.38	8.4	101
12	985	1020	acid	+	++	16.20		13.59	83.9	0.69	4.3	12.90	79.6	0.65	4.0	0.10	0.6	0.41	2.5	1.45	9.0	101.4
13	1510	1015	acid	+	+	17.35		14.86	85.7	0.89	5.1	13.97	80.6	0.66	3.8	0.00	0.0	0.42	2.4	1.41	8.1	101
14	910	1017	acid	+	0	11.58		9.88	85.3	0.29	2.5	9.59	82.8	0.43	3.7	0.00	0.0	0.29	2.5	0.98	8.5	101
15	1050	1012	acid	+	++	17.14		14.21	82.9	0.70	4.1	13.51	78.8	0.74	4.3	0.16	0.9	0.45	2.6	1.58	9.3	100.5
16	1125	1015	acid	+++	+	11.30	0.88	9.28	89.1	0.45	4.3	8.83	84.8	0.51	4.9	0.06	0.6	0.31	3.0	0.26	2.4	101
17	1110	1011	acid	+++	++	9.60	0.65	6.93	82.7	0.34	4.3	6.59	82.9	0.37	4.5	0.08	1.0	0.25	3.1	0.32	4.2	100.5
18	1700	1013	acid	+++	+	15.64	0.14	12.88	83.0	0.34	2.2	12.54	80.8	0.36	2.3	0.07	0.5	0.41	2.7	1.78	11.5	99.5
19	1260	1017	acid	+++	++	13.45	0.43	11.29	86.7	0.48	3.7	10.81	83.0	0.60	4.6	0.19	1.5	0.35	2.7	0.59	4.5	99
20	770	1019	acid	+	+	9.69		8.45	87.3	0.29	3.0	8.16	84.3	0.45	4.5	0.12	1.2	0.24	2.5	0.43	4.5	99

TABLE 9—URINARY ANALYSIS, CASE 19

Day of Disease	Volume c c	Sp Gr	Reaction	Total N Gm	Gloss Urea N Gm	Gloss Urea N %	NH₃ N Gm	NH₃ N %	Urea N Gm	Urea N %	Kreatinin N Gm	Kreatinin N %	Kreatin N Gm	Kreatin N %	Uric Acid N Gm	Uric Acid N %	Rest N Gm	Rest N %	Temp	Kreatinin Coefficient
20	325	1018	acid	4 29	3 46	80 8	0 224	5 24	3 23	75 6	0 228	5 34	0		0 065	15	0 529	12 3	102 8	5 4
21	300	1021	acid	3 50	2 96	87 3	0 122	3 49	2 84	81 1	0 212	6 05	0		0 02	59	0 304	8 7	104 8	5 0
22	250	1023	acid	3 29	2 88	87 3	0 092	3 2	2 77	84 1	0 17	51	0	.	0 015	46	0 232	7 0	99	4 0
23			Urine Lost																	
24	265	1017	acid	2 81	2 40	85 6	0 098	3 4	2 30	82 1	0 186	6 6	0		0 018	66	0 201	7 1	101 2	4 5
25	300	1022	acid	3 19	2 82	88 1	0 091	2 8	2 73	85 3	0 24	7 5	0		0 021	67	0 116	3 6	101	6 0
26	315	1023	acid	4 04	3 09	76 3	0 148	7 6	2 93	72 7	0 21	52	0		0 063	1 6	0 683	16 8	98 6	5 0
27	300	1020	acid	3 70	2 90	78 7	0 19	51	2 71	73 6	0 216	58	0		0 014	39	0 588	15 04	98 2	5 2
28	320	1022	acid	3 46	2 94	84 3	0 17	49	2 77	79 4	0 217	62	0		0 013	39	0 316	9 06	100 2	5 4
29	300	1020	acid	2 74	2 20	80 2	0 14	51	2 06	75 1	0 19	69	0 013	47	0 02	73	0 319	11 6	100 2	4 7
30	300	1020	acid	3 33	2 58	77 9	0 17	50	2 42	72 8	0 2	60	0 024	72	0 06	1 86	0 452	13 5	98 2	4 9
31	265	1020	acid	3 25	2 57	79 3	0 19	58	2 39	73 5	0 18	54	0 021	65	0 034	1 04	0 442	13 6	98	4 6
32	310	1024	acid	3 75	2 99	79 8	0 20	5 3	2 79	74 5	0 214	57	0 009	24	0 045	1 20	0 491	13 0	98 6	5 0
33	300	1018	acid	3 29	2 69	81 4	0 18	55	2 51	75 9	0 20	61	0		0 06	1 9	0 347	10 5	98 6	4 9
34	275	1020	acid	3 18	2 58	81 4	0 22	7 0	2 36	74 4	0 2	63	0		0 09	28	0 3	94	98 4	4 9
35	295	1019	acid	3 18	2 78	81 0	0 21	66	2 37	74 4	0 2	65	0		0 079	25	0 32	100	99	4 9
36	290	1016	acid	2 37	1 87	79 3	0 22	9 0	1 66	70 2	0 2	7 0	0		0 021	0 9	0 3	12 7	98 4	4 9
37	305	1022	acid	3 29	2 38	72 4	0 32	97	2 06	62 7	0 2	61	0		0 018	55	0 69	20 9	98 6	4 9
38	295	1013	acid	2 56	1 91	74 6	0 24	9 1	1 67	65 4	0 18	7 0	0		0 06	25	0 4	15 8	98 6	4 6
47	?	1012	acid	?	?	77 4	?	8 7	?	68 7	?	50	0		?	171	?	158	98 6	
48	305	1011	acid	2 11	1 59	75 4	0 19	9 1	1 4	66 3	0 14	66	0		0 031	148	0 347	164	99 0	3 4
49	570	1008	acid	3 46	2 82	81 4	0 35	100	2 47	71 4	0 19	53	0		0 016	46	0 44	127	98 0	4 6

stupor, frequent vomiting, rapid emaciation and incontinence of urine Several blood cultures were negative Widal positive Lumbar punctures were several times performed on account of meningeal symptoms

On account of vomiting and stupor the patient received very little nourishment, and toward the end of the febrile period was in a state of almost complete starvation, the stomach retaining nothing After defervescence, delirium, vomiting and incontinence continued and the patient remained in a very critical condition About the twenty sixth day the temperature fell, there was some slight improvement in the pulse and mental condition, and incontinence ceased, but the patient still refused food or vomited most of that ingested At this time the weight was 89 pounds After the twenty-sixth day the patient began to retain some pasteurized milk On the thirty seventh day 100 gm of chicken, 60 gm bread, 25 gm butter and 55 gm egg were taken (N, 4 91 gm , calories, 596) and similar food was offered thereafter, but was partly refused or vomited The observations terminated when the patient, in a very weak condition, weighing 94 pounds, was taken to the country She eventually recovered Although extreme care was observed it was found impossible, using the catheter every 4 to 6 hours, to collect all the urine, small portions of which were frequently lost Yet the portions lost were carefully estimated and were not large, so that the total amount obtained on days when none was lost did not vary greatly from that of other days, and constant relative anuria clearly existed While realizing that this deficiency vitiates the observations on total nitrogen, we do not believe the error from this source to be large

With this reservation we may note several interesting features in this case First, a state of advanced starvation existed toward the end of the febrile period, during which, with very low total N, the urea N remained unusually high and the ammonia N and the rest N relatively low, suggesting that the presence of fever may eliminate the usual features of the nitrogen partition of starvation Second, a considerable rise in the ratio of urea N during the twentieth to twenty second days indicated an improvement in metabolism in spite of a sharp exacerbation of fever, this improvement heralding a rapid defervescence Third, the steady decline in urea N ratio and rise in the ammonia N during convalescence suggests the appearance of starvation acidosis Fourth, the striking increase in the rest N on the thirty-seventh day followed the addition to the diet of meat and eggs and suggests that the organism was unable to metabolize properly the products of digestion of this rich protein food At the same time the pulse was accelerated 15 to 20 beats, the temperature rose 2° on the thirty-ninth and fortieth days, and the patient was less comfortable and vomited occasionally

CASE 20 —*Patient* —Woman, aged 20, weight on fifty ninth day, 78 pounds, admitted on the fifteenth day of disease to New York Hospital, service of Dr Conner, Aug 29, 1908 The patient ran through a very severe attack of typhoid fever, complicated by extensive hemorrhages The temperature from the fifteenth to the twenty second day reached 104 to 105 F , falling during the days of hemorrhage (nineteenth and twentieth of illness) After a short remission on the twenty-fourth day it rose again and continued above 104 until the present observations began, when its course is indicated in the table Incessant vomiting nullified all attempts at feeding Two large hemorrhages reduced the hemoglobin to 30 per cent and left the patient in a critical condition for several days The return of fever was accompanied by vomiting, excessive tympanites, a very low nervous state, repeated small bleedings with involuntary stools, and consolidation of the lower lobe of right lung, twenty seventh day

At the beginning of the urinary analyses the patient was taking very little nourishment, vomited occasionally and was extremely feeble The pulse did not fall to 100 until the forty sixth day On the thirty-second to thirty fourth days she retained a little barley water, on the thirty third day 50 gm of lactose were

TABLE 10 — URINARY ANALYSES, CASE 20

Day of Disease	Volume	Sp Gr	Reaction	Albumin	Indican	Total N Gm	Gross Urea N Gm	Gross Urea N %	NH$_3$ N Gm	NH$_3$ N %	Urea N Gm	Urea N %	Kreatinin N Gm	Kreatinin N %	Kreatin N Gm	Kreatin N %	Uric Acid N Gm	Uric Acid N %	Rest N Gm	Rest N %	Temp
32	1575	1003	acid	+	+	5.37	4.07	75.9	0.53	9.9	3.53	66.0	0.25	4.6	0.106	2.0	0.117	2.2	0.868	15.3	103.6
33	1440	1004	acid	++	O	4.83	3.92	80.9	0.29	8.0	3.52	72.9	0.188	3.9	0.199	4.1	0.161	3.3	0.372	7.7	102.6
34	1145	1005	acid	+	O	4.81	3.78	78.6	0.33	6.7	3.45	71.8	0.146	3.0	0.167	3.5	0.085	1.8	0.633	13.1	102.8
35	2096	1002	acid	O	O	4.82	3.98	82.5	0.44	9.1	3.54	73.4	0.21	4.3	0.18	3.7	0.08	1.7	0.37	7.7	102
36	1280	1004	acid	O	O	3.58	2.53	70.7	0.26	7.3	2.27	63.4	0.15	4.0	0.099	2.7	0.05	1.4	0.757	21.2	103.4
37	1100	1007	acid	+	O	4.82	3.08	64.0	0.155	3.2	2.93	60.8	0.21	4.3	0.185	3.8	0.065	1.3	1.28	26.5	101.2
38	1125	1004	acid	+	++	*		74.4		12.3		62.1		4.9		4.0		2.8		13.8	100.4
39	910	1005	acid	++	++	3.71	2.63	71.0	0.43	11.5	2.21	59.5	0.19	5.0	0.27	7.3	0.1	2.7	0.51	13.8	100.6
40	770	1004	acid	O	++	3.49	2.69	77.0	0.5	14.5	2.18	62.5	0.15	4.2	0.155	4.4	0.1	3.1	0.388	11.2	101
41	600	1010	acid	+	O	4.24	3.24	76.4	0.47	11.0	2.77	65.3	0.19	4.4	0.111	2.6	0.127	3.0	0.575	13.5	100.8
42	700	1005	acid	+	O	*		75.7		13.2		62.5		3.7		3.8		2.4		14.3	100.2
43	700	1007	alk	+	O	3.21	2.51	78.3	0.57	17.8	1.94	60.5	0.13	3.9	0.104	3.2	0.084	2.6	0.384	12.1	100.2
44	970	1003	acid	O	O	3.88	3.23	83.2	0.262	6.7	2.97	76.5	0.18	4.7	0.025	0.6	0.087	2.2	0.355	9.1	99.6
45		?				*															
46	350	1016	acid	O	++	2.81	2.24	79.3	0.301	10.6	1.94	68.6	0.143	5.0	0.011	0.4	0.092	3.2	0.344	12.0	99.8
47	400	1023	acid	O	O	4.51	3.52	77.8	0.414	9.1	3.10	68.7	0.184	4.0	0.014	0.3	0.16	3.5	0.645	14.2	99.8
48	555	1016	acid	O	++	4.35	3.51	80.7	0.40	9.2	3.11	71.5	0.164	3.7	0.053	1.2	0.12	2.7	0.501	11.5	99.8
49	650	1013	acid	O	O	4.05	3.20	79.2	0.292	7.2	2.91	72.0	0.156	3.8	0.025	0.6	0.087	2.1	0.575	14.1	99.8
50	750	1014	acid	O	O	4.56	3.81	83.6	0.48	10.5	3.34	73.1	0.176	3.8	0.022	0.5	0.115	2.5	0.436	9.5	99.2

* Incomplete

TABLE 11 — Urinary Analyses, Case 21

Day of Disease	Volume	Sp Gr	Albumin N Gm	%	Total N, Gm	Gross Urea N Gm	%	NH₃ N Gm	%	Urea N Gm	%	Kreatinin N Gm	%	Kreatin N Gm	%	Uric Acid N Gm	%	Rest N Gm	%	Indican	Reaction	Temp
7	562	1028	1.600	13.7	10.1	8.7	86.14	0.764	7.56	7.94	78.58	0.421	4.17	0.073	0.72	0.135	1.34	0.77	7.63	+++	acid	104.8
8	650	1024	1.8	13.64	11.3	9.9	87.56	1.03	9.18	8.43	78.38	0.47	4.12	0.067	0.59	0.137	1.21	0.745	6.52	++	acid	104.4
9	500	1023	0.16	1.8	8.23	6.3	82.4	0.637	7.7	6.16	74.7	0.257	3.12	0.143	1.73	0.137	1.36	0.938	11.39	0	acid	103.0
10	720	1011	0.11	0.69	6.13	5.05	82.4	0.756	12.32	4.29	70.08	0.317	5.17	0.180	2.93	0.16	2.61	0.422	6.89	0	acid	101.8
11	1365	1004	0.068	0.96	7.03	5.73	81.5	0.75	10.67	4.98	70.83	0.32	4.56	0.212	3.01	0.158	2.25	0.609	8.68	+	alk	101.6
12	1775	1005	0.21	2.903	7.01	5.66	81.0	0.505	7.2	5.17	73.8	0.422	6.02	0.18	2.57	0.185	2.64	0.542	7.77	0	acid	102
13	1215	1007	Trace		6.56	5.42	81.46	0.62	9.27	4.8	72.19	0.4	6.0	0.157	2.36	0.16	2.5	0.51	7.68	0	acid	101.4
14	1375	1005	Trace		5.88	5.00	81.8	0.413	8.46	3.58	73.34	0.29	5.92	0.165	3.38	0.055	1.13	0.38	7.77	+	acid	101.4
15	1175	1004	Trace		4.84	3.84	79.28	0.398	8.22	3.43	71.04	0.288	5.95	0.059	1.22	0.05	1.05	0.607	12.52	+	acid	100.2

TABLE 12 — Urinary Analyses, Case 22

Day of Disease	Volume cc	Sp Gr	Reaction	Total N, Gm	Albumin N, Gm	Gross Urea N Gm	%	Amm N Gm	%	Urea N Gm	%	Kreatinin N Gm	%	Kreatin N Gm	%	Uric Acid N Gm	%	Rest N Gm	%	Pulse	Temp	General Condition
22	2700	1017	acid	29.70	0.783	25.650	88.70	1.296	4.48	24.354	84.22	0.459	1.59	0.173	0.60	0.364	1.26	2.271	7.85	124	102.4	Apathy Incontinent
23	2810	1015	acid	28.90	0.815	23.850	84.90	1.221	4.35	22.629	80.55	0.496	1.77	0.072	0.26	0.227	0.81	3.440	12.26	124	102.8	Brighter
24	1110	1017	acid	11.910	0.170	12.725	88.10	0.721	4.09	12.004	83.11	0.236	1.63	0.080	0.55	0.157	1.09	1.242	8.63	116	102.0	Subsultus
26	2012	1016	acid	21.885	0.215	18.620	86.00	1.154	5.30	17.466	80.70	0.384	1.78	0.065	0.30	0.278	1.28	2.293	10.64	120	102.0	Brighter, restless
27	1600	1016	acid	16.605	0.285	13.470	82.54	0.896	5.49	12.574	77.05	0.341	2.09	0.059	0.36	0.282	1.73	2.168	13.28	110	101.6	Brighter, restless
28	1530	1017	acid	15.617	0.215	13.005	84.70	0.880	5.71	12.125	78.39	0.298	1.93	0.028	0.18	0.230	1.50	1.861	12.09	116	101.6	Much better, hungry
29	1550	1016	acid	15.015	0.175	12.137	81.54	1.015	6.80	11.122	74.74	0.279	1.87	0.078	0.52	0.220	1.47	2.174	11.60	120	99.6	Improving

Diet Twenty third to twenty ninth day, milk 50 oz, lactose 300 gm, N 7.7 gm, Cal 3368

given but vomited, on the thirty-fourth day 75 gm of lactose (300 calories) were retained On the thirty-fifth day she took scraped beef 1 ounce, beef juice 0 5 ounce and 190 gm lactose (N, 1 gm , calories, 785), and on the thirty-sixth day one egg, ice cream, 6 ounces, broth, 6 ounces, toast, 25 gm , beef juice, 2 ounces, lactose, 125 gm (N 1 8 gm , calories, 910) Thereafter a somewhat similar diet was maintained under which very slow improvement began Discharged cured, seventy-fifth day

In this case our observations cover the terminal febrile period and beginning convalescence of a remarkably severe typhoid fever During the entire period the patient was reduced to an extremely low state of vitality, in which typhoid intoxication, pneumonia, anemia and starvation were combined The very low total nitrogen we refer to this general condition On account of incontinence the urine was drawn by catheter The first analysis gave low urea, considerable ammonia and rather high rest nitrogen, which accord with the usual findings of severe febrile stages of typhoid fever The later fall in urea we are inclined to refer in part to starvation acidosis On the thirty-fifth day the addition to the diet of scraped beef and beef juice was followed by a striking increase in the rest N, indicating, as in Case 19, that the organism was unable to metabolize the products of digestion of this protein food The considerable excretion of kreatin accords with the extreme loss of flesh As improvement set in the kreatin diminished

CASE 21 —*Patient* —Woman, aged 38, weight on twenty-ninth day 107 pounds, admitted Oct 1, 1908, to New York Hospital, service of Dr Conner The patient ran through a typical sharp attack of typhoid fever lasting 28 days The chief feature was the temperature, which reached 104 2° on the third day, and remained constantly between 104° and 106° until the eighth day There was rapid loss of flesh, considerable diarrhea and abdominal pain but no grave symptoms The diet consisted of small quantities of meat broth, custard, gelatin and lactose Beginning on the fifth day, 75 to 100 gm of lactose were given, on the eighth day, 115 gm , ninth to eleventh days, 45 gm , twelfth day, 70 gm , thereafter about 200 gm On the thirteenth day the estimated calories of the diet were 2,064, which was maintained The patient made a quick recovery

The urinary analyses show a high gross urea ratio, low rest N and very favorable course, notwithstanding the high fever The low total N may be referred to the carbohydrate diet which was instituted at the suggestion of Dr Conner to test the influence of this diet on the course of typhoid fever In spite of this diet the ammonia N reached or possibly exceeded the upper limits of a normal standard The indican was unusually low The albuminuria was partly the result of menstruation, but most of the urine was drawn by catheter

CASE 22 —*Patient* —Man, aged 26, admitted to House of Relief, service of Dr Conner, Feb 19, 1909, on the eleventh day of the disease The patient passed through a very severe attack of typhoid fever, the temperature for twenty-four days remaining between 101 and 105° F Constant apathy or stupor incontinence, subsultus were present until the twenty-fourth day, when the patient improved slightly Recovery was then rapid, but convalescence was interrupted by cystitis and multiple arthritis, which were attributed to the catheterizations On the forty-ninth day he weighed 115 pounds

The striking features of this case were the maintenance of a very high urea ratio during severe stages of the disease, and the prompt recovery Throughout the disease the patient took nourishment well From the eleventh to twenty-second days the diet consisted of milk, 60 ounces and lactose 300 gm (N, 9 3 gm calories, 2,350) Thereafter the diet was maintained as indicated in the table To Dr T F Laurie, house physician, we are indebted for very careful supervision of the case during the period of observation

NOTE —In addition to the articles cited in the text, the following may be consulted Ewing Proc Philadelphia Path Soc , 1905, new series, viii, 65 New York Med Record 1907, lxxi, 537

A STUDY OF THE MECHANICAL FACTORS IN EXPERIMENTAL ACUTE PULMONARY EDEMA *

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During recent years the rôle of chemical agents in the development of edema has received considerable attention and several theories have been propounded with a view of explaining all forms of edema on a chemical basis As a consequence the importance of mechanical factors has been somewhat discredited Previous studies of the mechanical agents in acute pulmonary edema would indicate that here the phenomena may be explained on a mechanical basis A continuance of these studies might, therefore, be of interest in order to determine whether pulmonary edema the result of other means than those previously employed could be explained without the aid of chemical agents

In an exhaustive article published in 1878, William H Welch[1] made the first attempt to explain, on an experimental basis, the phenomena of acute pulmonary edema Working with rabbits he determined that ligation of the thoracic aorta, in such a manner that the only outlet was the left carotid and left subclavian, produced uniformly in animals with strong hearts a marked pulmonary edema In animals with presumably weak hearts, as shown by the failure to respond to a rise in the pulmonary blood pressure, edema did not occur He also determined that pulmonary edema could be produced by marked constriction of the pulmonary vein or compression of the left ventricle to the extent that its capacity was reduced 75 per cent He noted that all of these procedures caused a marked rise in pressure in the pulmonary artery, which he considered a very important factor in the development of edema Welch formulated the results of his experimental work in the following words "Mechanical edema is the result of a disproportion between the working power of the left ventricle and the right ventricle of such a character that, the resistance remaining the same, the left heart is unable to expel in a unit of time the same quantity of blood as the right heart " This explanation of pulmonary edema gave as the important factor passive congestion in the pulmonary artery Welch's theory called forth consid-

1 Welch, W H   Zur Pathologie des Lungenodems Virchow's Arch f path Anat , 1878, lxxii, 375

eiable ciiticism, especially fiom clinicians who attempted to apply this explanation to acute pulmonaiy edema in man Sahli called attention to the absence of evidence of intense hyperemia in pulmonary edema, especially in nephritic and cachectic conditions Welch answers this criticism by saying that the color of diopsical tissues is an unsafe guide as to their blood content, as a pale dropsical lung may be markedly hyperemic Especial stress has been laid on the character of the pulse duiing an attack While usually small and iapid, it is at times normal or even of high tension (Sahli,[2] Hewlett,[3] Riesman,[4] Crummei[5]) The presence of high pressure has been used as an aigument against impaired activity of the left ventricle Welch's reply to this criticism was that complete paralysis of the left ventiicle is not necessary to cause a disproportion between the working power of the two ventricles

Welch's experiments weie iepeated by Mayei,[6] Sahli[2] and Lowit[7] Mayer obtained the same results, but considered the iise in systemic piessure to be due to vascular spasm excited by the cerebral anemia Sahli, woiking with dogs instead of rabbits, was able only infrequently to produce edema, which he explained by the greater permeability of the vessel walls in iabbits, and this factor iather than mechanical agents he considers responsible foi the edema Lowit, in repeating the experiments, obtained the same results, but considers overfilling of the pulmonary vessels as an impoitant element By taking the pressure in the left auricle and at the same time in the pulmonaiy and systemic ciiculation, he made the interesting observation that an increase in the pulmonary artery may be associated with lessened pressuie in the left auricle or *vice veisa,* that is, that direct transmission of pressuie through the pulmonary artery to the pulmonary vein does not necessarily occur

Both Lowit and Bettelheim[8] were able to produce pulmonary edema by ligating the left coronary artery, the edema being associated with a fall in the systemic and a rise in the pulmonary pressuie

2 Sahli, H   Zur Pathologie und Therapie des Lungenodems   Arch f expei Path u Pharmakol , 1885, xix, 431

3 Hewlett, H M   Four cases of acute suffocative pulmonary edema   Inteicolonial Med Jour , Australasia, 1903, viii, 611

4 Riesman, D   Acute pulmonary edema, with special reference to a iecurrent form   Tr Assn Am Phys , 1906, xxi, 155

5 Crummer, L   Acute suffocative pulmonaiy edema   Northwestern Lancet, 1902, xxii, 203

6 Mayer, S   Verhandl d Akad d Wissench Wien , 1878, lxxvii, 266

7 Lowit, M   Ueber die Entstehung des Lungenodems   Beitr z path Anat u z allg Path , 1893, xiv, 401

8 Bettelheim, J   Ueber die Storungen der Herzmechanik nach Kompression der Arteria Coronaria sinistra des Lungenodems   Ztschr f klin Med , 1887, xii, 550

Grossman[9] and Lowit produced pulmonary edema in dogs by intravenous injection of muscarin nitrate Grossman reported a fall in the systemic pressure, with a temporary fall followed by a rise in the pulmonary artery He explains these blood-pressure changes by a selective action of the drug causing spasm of the left ventricle He calls attention, however, to a few instances in which the rise appeared earlier in the pulmonary artery than in the left auricle, a phenomenon which could not be explained by stasis in the left heart As Brunton had stated that muscarin may constrict the pulmonary artery, Grossman cut the cord, but found that this did not interfere with the primary rise in the pulmonary artery Brodie and Dixon[10] have recently shown that muscarin dilates rather than constricts the pulmonary artery Lowit was able to produce pulmonary edema with muscarin His results differ from Grossman in that almost invariably the rise in pressure appeared earlier in the pulmonary artery than in the left auricle and therefore, stasis arising from spasm of the left ventricle could not be the cause Grossman and Lowit agree that evidence of disproportion between the working power of the two sides of the heart develops, but that the cause of this disproportion is still undetermined Muscarin edema has a direct clinical bearing as in poisoning with toadstools (*Agaricus muscarinus*) pulmonary edema is a prominent symptom Pilocarpin, which resembles muscarin in its action, has probably been responsible for many attacks of pulmonary edema in nephritics Tyson[11] refers to the frequency with which pulmonary edema appeared at the time it was customary to administer large doses of pilocarpin in kidney cases

Lowit has studied very carefully the blood-pressure changes associated with acute pulmonary edema produced by acetic ether He found, immediately after the intravenous injection of a small amount a decided fall in the systemic blood pressure and simultaneously with this a rapid fall in the pressure in the pulmonary artery followed by cardiac standstill Since these pressure changes do not show any evidence of stasis Lowit considered that he had demonstrated that acute experimental pulmonary edema could be produced independently of mechanical agents As supporting this view, he has been able to cause quite extensive transudation into the peritoneal cavity by the intraperitoneal injection of butyric ether

9 Grossman, M   Das Muscarin Lungenodem Ein Beitrag zur Lehre von der Entstehung des acuten Allgemeinen Lungenodems Ztschr f klin Med , 1887 xii 550

10 Brodie T G and Dixon W E   Contributions to the physiology of the lungs Jour Physiol London 1904 xxx 476

11 Tyson J   A discussion of Riesman s paper on acute pulmonary edema Tr Assn Am Phys 1906 xxi, 175

Guinaid and Teisser[12] demonstrated typical pulmonary edema in rabbits after the intravenous injection of 30 mg of methyl salicylate, the observed pressure changes corresponding to those seen after the use of muscarin

Von Zeissl[13] by intravenous injection of Lugol's solution into dogs was able to produce very extensive pulmonary edema During the development of the edema the pulmonary pressure always rose, the systemic pressure varied, at times a rise, at other times a fall, and, as had been observed with acetic ether, pressure changes in the left auricle that were apparently independent of that in the pulmonary artery The right ventricle dilated, the left remained normal or became contracted Although these pressure phenomena showed the presence of stasis, he considers changes in the vessel walls as probably an important factor in the development of the edema

Finally, there is the experimental work of Powkusky[14] with carbonic oxid He was able to cause extensive edema in dogs and rabbits by this means Blood-pressure measurements were not made, but he reports that during the experiment the left side of the heart appeared empty and contracted, the right heart full and dilated and the pulmonary arteries distended with blood—precisely the appearance that had been noted after acetic ether and iodid

Summarizing the cardiovascular changes observed in the pulmonary edema produced by these various chemical agents, we notice a striking similarity Generally there is a fall in the systemic pressure and a rise in pressure in the pulmonary artery At the same time the right side of the heart becomes dilated, the left remains normal in size or, as some have maintained, contracted Pressure changes in the pulmonary artery are not necessarily associated with corresponding changes in the left auricle, since a rise in pressure in the pulmonary artery may be associated with a fall in pressure in the left auricle or *vice versa*

EXPERIMENTAL OBSERVATIONS

Our experimental work was undertaken with a view of determining the following questions first, whether acute pulmonary edema, produced by other agents than those already tried, is associated with a rise in

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12 Guinaid, S , and Teisser, J   Nouvelles recherches expérimentales sur la pathogénie de l'oedème aigu du poumon Jour de physiol et de path gén , 1901, iii, 42

13 Van Zeissl, M   Ueber Lungenodem in Folge von Jodintoxication Ztschr f klin Med , 1895, xxvii 363

14 Powkuskv, W   Ueber die Veigiftung mit Kohlenoxydgas Virchow's Aich f path Anat , 1869, xxx 524

pressure in the pulmonary artery, second, to repeat the experiments with acetic ether, since in the previous work the acetic ether had been an exception, inasmuch as it produced pulmonary edema without an increase in pressure in the pulmonary artery, third, the value of various agents in controlling the development of modifying the course of acute experimental pulmonary edema

Nitric oxid, ammonia vapors and illuminating gas are all recognized as causing acute pulmonary edema in man Hall[15] reports three cases of edema in firemen exposed to the fumes of nitric oxid, and pulmonary edema under similar circumstances[16] has been noted with ammonia vapors Adrenalin often produces a pulmonary edema in rabbits, and Sahli refers to the frequency with which pulmonary edema occurs in dogs poisoned by hydrocyanic acid These various agents were employed in our work and, in addition, the effect of artificial mitral stenosis on the pulmonary circulation Dogs were used in most of our experimental work In a few cases rabbits were utilized instead Ether was used as an anesthetic Artificial respiration was maintained by a bellows and motor The pressure in the pulmonary artery was determined by a mercury manometer, the descending arm of which had twice the diameter of the ascending arm, in this way slight changes in pressure could be more readily detected The cannula was tied in the branch of the left pulmonary artery supplying the upper or middle lobe The systemic pressure was taken from the right carotid Pulmonary edema was considered present when froth either issued from the trachea or could be expressed freely from the large bronchi by moderate compression of the lung

Nitric Ovid —Nitric oxid was generated from a mixture of metallic copper and nitric acid The fumes were forced from the flask in which they were generated into the tracheal tube, where they became mixed with the ether vapor As soon as a small amount of the gas had been inhaled, there was a very decided fall in the carotid pressure with a very slight fall in pressure in the pulmonary artery The carotid pressure soon reached a level at which it remained stationary, but the pressure in the pulmonary artery steadily continued to fall If the amount of gas was suddenly increased, there was at once a fall in pressure in both arteries Eight minutes after beginning the gas, bradycardia and arrhythmia were noted, followed by cardiac standstill There was no evidence of unilateral dilatation of the heart at any time The lungs

15 Hall, J M, and Cooper, C E   The effects of inhalations of the fumes of nitric acid, with report of cases Jour Am Med Assn, 1905, xlv, 396

16 Several cases of this character occurred in firemen fighting the flames in a refrigerator plant at the stockyards in Chicago

showed very marked hemorrhagic edema, blood-tinged froth issued from the trachea Here, as in all other edemas, the lower lobes were most extensively involved, the posterior median portion of the middle lobe less edematous, the remainder of the middle lobe still less involved The upper lobes usually showed a slight patch in the posterior median portion The lobe supplied by the branch of the pulmonary artery which contained the cannula was always free from edema

The changes in blood pressure are shown in Table 1

TABLE 1 —CHANGES IN BLOOD PRESSURE WITH NITRIC OXID

Time	Carotid Pressure	Pulmonary Artery Pressure	Remarks
	110	13 5	Before giving nitric oxid
36 seconds	66	11 0	After beginning nitric oxid
72 seconds	60	9 0	Inhaling nitric oxid continuously
250 seconds	56	8 0	Inhaling nitric oxid continuously
300 seconds	32	6 0	Amount of nitric oxid increased
480 seconds	0	0 0	Very marked pulmonary edema

At no time throughout the course of this experiment was there an increase in pressure in the pulmonary artery To consider a disturbance in the ratio between the two pressures as of importance in supporting Welch's theory is more or less fallacious, as drugs like nitroglycerin cause a very marked fall in the carotid pressure without affecting the pressure in the pulmonary artery If mere disturbance of the ratio was an important factor, pulmonary edema would develop under these circumstances In this experiment of producing acute pulmonary edema by means of nitric oxid, we were unable to detect any evidence of disproportion in the work of the two sides of the heart The pulmonary pressure steadily fell There were no signs of overdistention of any single cardiac chamber, or of one side of the heart For this reason it would be impossible to apply Welch's theory to explain the development of the edema It would appear that irritation of the bronchial or alveolar epithelium or the underlying vessels was an important factor Cohnheim and Lichtheim demonstrated that in animals in which they had produced a hydremic plethora by transfusion, irritation of the skin with iodin or exposure to the sun was sufficient to produce a local edema We must bear in mind that in Cohnheim's experiments a predisposition to edema was present Whether such a predisposing factor is essential in the lungs, it would be impossible to say There is no evidence in any case that this predisposing factor is a disproportion in work of the two ventricles

Ammonia Vapor —The results obtained by inhalation of ammonia vapors were similar to those produced by the nitric oxid It was neces-

sary, however, to expose the animal for a much longer period of time, the edema was less marked and of the pale type.

Carbon Monoxid—When the gas was administered slowly the carotid pressure was very slightly lowered, the pressure in the pulmonary artery unchanged or at times showed a very slight rise When the gas was administered more freely, a point was reached where the systemic pressure dropped suddenly to zero, with extreme slowing followed promptly by cardiac standstill During this time the pressure in the pulmonary artery rapidly fell, standstill of both ventricles occurring at the same time If the flow of gas was stopped, the heart gradually returned to normal In none of our attempts, either by prolonged slow administration or the free use of the gas, were we able to produce a pulmonary edema, although, following Powkowsky's advice, young dogs were used The experiment was repeated on rabbits, they appeared much more tolerant of the gas than dogs, prolonged free inhalation was required to bring about cardiac standstill and the lungs were free from involvement

Hydrocyanic Acid—Sahli referred to the frequency of pulmonary edema in dogs after poisoning with hydrocyanic acid In Germany it is apparently a practice among veterinarians to kill incurable or suffering dogs in this way Sahli unsuccessfully attempted to produce pulmonary edema in rabbits with the hydrocyanic acid We used the dilute acid of the U S Pharmacopeia This we administered in various ways by mouth, directly into the stomach, subcutaneously and intravenously, but were unable to produce even a moderate pulmonary edema There was a slight fall in the carotid pressure, the pulmonary pressure remaining unchanged or showing a very gradual lowering, except in one animal in which we obtained a drop of 30 mm Hg in the carotid pressure with a rise of 3 mm Hg in the pulmonary artery, independent of any struggling without, however, producing an edema This single case is suggestive on account of the evidence of disproportion of work between the two sides of the heart With stronger solutions or in certain animals this difference in pressure might reach a sufficient degree to give rise to a pulmonary edema

Iodids—Lugol s solution was used in these experiments, in the first series of 10 per cent, in the second series a 50 per cent, and in the third series the undiluted solution In Series 1 the animal received intravenously 200 c c of the 10 per cent solution within a period of twenty minutes There was a sharp rise in the carotid pressure immediately after the injection was begun, this high pressure being maintained until about 180 c c had been injected following this there was a rapid fall and cardiac standstill Toward the end the heart became irregular, long

vagus strokes appeared and continued until the end After the injection
of 100 c c there was a gradual rise in pressure in the pulmonary artery,
which was maintained during the beginning of the fall in the carotid
pressure (Table 2)

TABLE 2 —CHANGES IN BLOOD PRESSURE WITH 10 PER CENT LUGOL'S SOLUTION

Time	Carotid Pressure	Pulmonary Pressure	Remarks
	130	30	Previous to giving Lugol's sol
30 seconds	150	32	Transfusion with 10% Lugol's sol
270 seconds	175	40	Had received 100 c c Lugol's sol
900 seconds	180	44	Had received 150 c c Lugol's sol
1200 seconds	50	40	Had received 180 c c Lugol's sol
1320 seconds	0	0	Very slight pulmonary edema

During the rise in pulmonary pressure the right ventricle and right
auricle dilated, the left ventricle and auricle remained normal in size
throughout the experiment The lungs showed a moderate degree of
hemorrhagic edema

In the second series the animal received 60 c c of a 50 per cent
Lugol's solution, in doses of 20 c c each, extending over a period of
eleven minutes The animal was a young dog weighing 5 kilos During
the preparation the blood pressure became very low After the first dose
of Lugol's solution there was a distinct rise in the carotid pressure, which
was maintained until the animal had received 60 c c , then the long
vagus stroke appeared and the blood pressure fell rapidly This was asso-
ciated with a distinct rise in the pressure in the pulmonary artery,
which was maintained until the end (Table 3)

TABLE 3 —BLOOD PRESSURE WITH 50 PER CENT LUGOL'S SOLUTION

Time	Carotid Pressure	Pulmonary Pressure	Remarks
	36	8	Previous to giving Lugol's sol
30 seconds	40	10	After 20 c c 50% Lugol's sol
300 seconds	48	11	After 20 c c 50% Lugol's sol
720 seconds	0	0	After 20 c c 50% Lugol's sol

The condition of the heart was the same as in the preceding experi-
ment Pulmonary edema was much more marked than in the first ex-
periment

In the third experiment the animal received three intravenous injec-
tions of 25 c c , each of undiluted Lugol's solution Immediately follow-
ing the first injection there was a marked rise in the carotid pressure
and at the same time a gradual rise in pressure in the pulmonary artery
(Table 4 and Tracing 1)

The carotid pressure quickly returned to the normal level to mount
up again after the second injection, the pulmonary pressure, however,
remaining high until just before death The carotid pressure following

the third injection remained unchanged, gradually falling later The heart was the same as in the preceding series, but the pulmonary edema was much more marked

TABLE 4 —BLOOD PRESSURE WITH UNDILUTED LUGOL'S SOLUTION

Time	Carotid Pressure	Pulmonary Pressure	Remarks
	90	10	Previous to giving Lugol's sol
30 seconds	110	34	After 25 c c Lugol's sol
180 seconds	120	36	After 25 c c Lugol's sol
300 seconds	70	36	After 25 c c Lugol's sol
540 seconds	52	32	
660 seconds	0	0	Very decided lung edema

These results are fully in accord with those of Van Zeissl Attention is called especially to the appearance of the heart dilatation of the right auricle and ventricle, the left auricle and ventricle normal Van Zeissl reported the left side of the heart contracted, with this we can
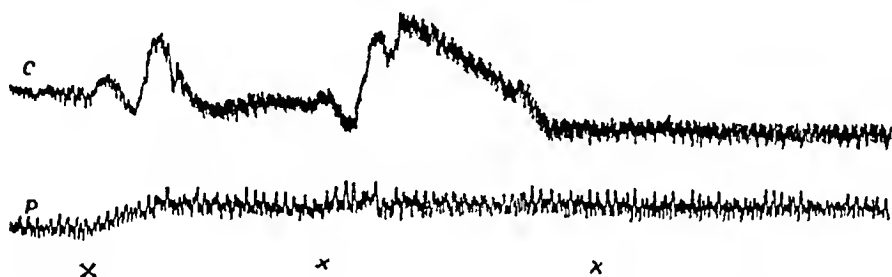
Tracing 1 —Showing effect on the carotid and pulmonary arterial pressure of the intravenous injection of undiluted Lugol's solution P, pulmonary, C, carotid, X, 25 c c of Lugol's solution injected

not agree, while compared with the right side it appeared small, the size of the chambers corresponded closely to that preceding the injection As Van Zeissl suggested that the rise in pulmonary pressure was due to constriction of the pulmonary artery, we used the various vasodilators without being able to lower the pulmonary arterial pressure In another animal the cervical cord and vagi were cut before giving the iodid, but the rise in pulmonary pressure occurred the same as in the untreated animal As our experience with acetic ether had shown that occasionally very large doses produced edema without a rise in pressure in the pulmonary artery, attempts were made to bring about the same results by using a very strong solution of iodin and potassium iodid In every instance, however, a rise in the pulmonary pressure was observed The mechanical factors favoring the development of edema were present, whether, however, they were responsible for the edema is questionable This matter will be considered more in detail in discussing the effects of acetic ether

Acetic Ethei —The inhalation or intravenous injection of a small amount of acetic ether invaiiably pioduces in dogs a typical pulmonary edema The acetic ethei was administered either by inhalation oi intia-venous injection to 17 dogs and produced an extensive hemoirhagic edema in every animal In our eaily experiments doses of 2 to 3 c c were injected into the femoral vein, later smaller doses of 0 5 to 1 c c were used Even with the smaller dose there is a distinct fall in the carotid pressure followed by a piompt partial recovery Each succeed-ing dose produces a similai effect until, finally, the heart stops suddenly With the very large doses occasionally death occurs without any rise in pressure in the pulmonary artery More frequently, however, and in-variably with the smaller doses, a very decided rise in piessuie was ob-served During the rise in the pulmonary arteiial pressuie, the right ventricle and auiicle became much dilated, but we were never able to observe any dilatation of the left auricle or left ventricle Pieceding the cardiac standstill there was maiked bradycaidia The left ventricle stopped first, quite regular pulsation of the iight ventricle could often be obseived one or two minutes after the left ventricle had ceased beat-ing In those animals also in which a rise in pulmonary arterial piessure did not occur, a very extensive edema was found, apparently as extensive as in those cases in which the pulmonaiy pressuie was increased, thus showing that an increase in the pulmonary pressure is not essen-tial foi the pioduction of edema When the acetic ether was inhaled the same phenomena were observed, with the exception that a iise in pul-monaiy arterial piessure always occuiied Tables 5, 6 and 7 show the blood pressure changes and the ratio between the caiotid and pulmonaiy pressure

TABLE 5 —EFFECT OF LARGE DOSES OF ACETIC ETHER

Time	Carotid Piessure	Pulmonary Arteiial Pressure	Ratio Between Caiotid and Pulm	Remaiks
	80	14	5 7	Beginning ether
60 seconds	44	9	4 9	Aftei 2 c c acetic ether
150 seconds	30	6	5 0	
270 seconds	14	3	4 6	After 1 c c acetic ether
450 seconds	42	12	3 5	
660 seconds	56	10	5 6	
720 seconds	11	3	3 6	After 2 c c acetic ether
750 seconds	0	0		Very marked edema

In the expeiiment shown in Table 5 we see the pulmonary pressuie nevei ieached the height it obtained befoie tieatment was instituted, though after the second injection of acetic ether there was a sharp rise in the pulmonaiy arteiial pressure, at which time it approachcd the original level The iatio between the blood piessuie in the two ventricles

shows that, following the second injection of acetic ether, the right ventricle was doing about one-third the amount of work done by the left ventricle, while, preceding the first injection, it was only doing about one-sixth as much work as the left ventricle Too much stress however, should not be placed on a disturbance in the ratio as a factor in the development of pulmonary edema Apparently an actual rise in the pulmonary pressure is essential rather than a disturbance in the relative amount of work done by the two chambers Whether a rise in the pulmonary pressure, which follows a fall and which does not reach the original level, as in the above table, can be looked on in the same light as an actual rise in pulmonary pressure appears to the writers very doubtful

TABLE 6 —ACETIC ETHER IN SMALL DOSES INTRAVENOUSLY

Time	Carotid Pressure	Pulmonary Arterial Pressure	Ratio Between Carotid and Pulm	Remarks
	84	9 0	9 2	Before receiving ether
20 seconds	64	10 5	6 3	After 1 c c acetic ether
60 seconds	68	13 5	5 0	
220 seconds	80	17 5	4 6	
300 seconds	70	15 0	4 6	20 s after 1 c c acct eth
480 seconds	36	12 0	3 0	30 s after 1 c c acct eth
540 seconds	0	0 0		Very marked edema

A very marked pulmonary edema was produced by the inhalation of acetic ether The rise and absolute height of the pressure in the pulmonary artery was greater than we have been able to produce by any other means Another peculiarity of this test was a *decided gradual rise in the pulmonary pressure without a fall in the carotid pressure* Later, when the amount of ether was increased, a very marked fall in carotid pressure took place

TABLE 7 —INHALATION OF ACETIC ETHER

Time	Carotid Pressure	Pulmonary Arterial Pressure	Ratio Between Carotid Pressure	Remarks
	108	24	4 5	Before acetic ether
120 seconds	108	32	3 5	2 min after beginning inhalation
240 seconds	40	32	1 2	4 min after beginning inhalation
360 seconds	80	40	2 0	6 min after beginning inhalation
480 seconds	54	44	1 2	8 min after beginning inhalation
600 seconds	104	48	2 1	Ether discontinued for one minute

As we had determined that pulmonary edema could be produced with large doses of acetic ether, without an increase in the pulmonary pres-

suie, it was impoitant to deteimine whethei with the small doses a rise in the pulmonaiy piessuie was essential for its development Auscultation over the lungs ievealed the piesence of numeious râles following the injection of small doses, and before a iise in pressure in the pulmonaiy aitery took place As a further test the heait and lungs weie quickly removed just at the moment a iise in the pulmonary pressuie was observed, in one instance within two seconds Under these cii cumstances marked pulmonary edema had already developed This experiment was iepeated several times with always the same iesult We must, theiefore, conclude that the rise in pressure in the pulmonaiy aiteiy ieally took place aftei the edema had appeaied

In endeavoiing to explain the inciease in the pulmonary arterial piessuie, without evidence of stasis in the left heait, the possibility that the edema might cause the iise in piessuie was consideied It is con-

Tracing 2 —Effect on the blood pressuie of small doses of acetic ethei injected intravenously P, pulmonary artery, C, caiotid, X, 1 c c of acetic ethei injected into the femoral vein Very marked pulmonary edema

ceivable that the piessuie exerted on the arteiioles of the pulmonary aiteiy by the distended alveoli might inciease the iesistance sufficiently to cause such a rise in piessuie The effect on the blood piessure of overdistention of the lung with aii was fiist tested We weie unable, however, even after piolonged distention, to pioduce a iise in the pulmonary blood piessure An attempt was then made to distend the alveoli by allowing water to flow slowly down the trachea An 8-kilo dog ieceived in this way 250 c c of water in a peiiod of 10 minutes After the instillation of 100 c c a gradual iise in the carotid piessuie was noted, which slowly increased until 175 c c had been given, when a gradual fall set in, which continued as long as the instillation of watei was kept up With the beginning of the iise in the caiotid pressuie, theie was a giadual increase in piessure in the pulmonary aiteiy, which ieached its maximum much later than the maximum rise in the carotid Following this there was a slight fall in pressure not commensurate, however, with the fall in the caiotid These blood-pressuie changes aie shown in Table 8 The lungs of this animal had the same appearance as those with pul-

monary edema   Abundance of bloody froth could be expressed from the large bronchi, and red blood corpuscles and granular material were found in the alveoli on microscopic examination   Apparently the instillation of water produced a pulmonary edema, and, therefore, the rise in pressure in the pulmonary artery was not necessarily due directly to the instillation of the water

TABLE 8 —EFFECT ON CAROTID AND PULMONARY PRESSURE OF INSTILLATION OF WATER INTO THE TRACHEA

Time	Carotid Pressure	Pulmonary Arterial Pressure	Remarks
	130	19 0	Before instillation began
200 seconds	156	22 0	After 125 c c of water
240 seconds	170	23 5	After 175 c c of water
330 seconds	90	26 0	After 200 c c of water
450 seconds	68	21 0	After 220 c c of water
600 seconds	10	17 0	After 250 c c of water
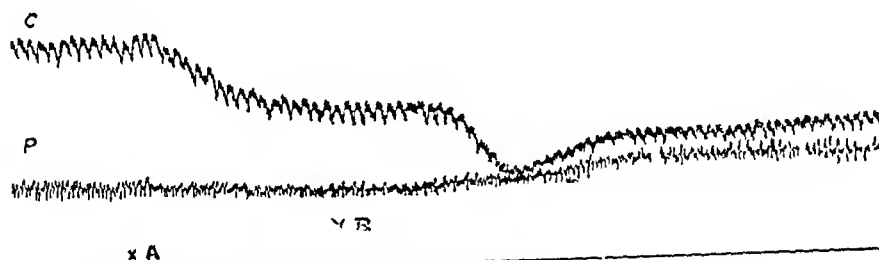
Tracing 3 —Showing the effect of acetic ether after section of the cord in the mid cervical region   A, cord cut, b, 1 c c acetic ether intravenously

From a study of the edema produced by iodids, we must conclude that with this agent, at least, the edema is not the cause of the rise in pressure in the pulmonary artery, as Van Zeissl determined that animals killed a few seconds after the increase in pulmonary pressure began did not show edema, but that prolonged increase in pressure was essential for its development   The rise in pressure in the pulmonary artery after acetic ether could not be prevented or modified by large doses of nitroglycerin   Combined section of the cord in the mid-cervical region and of the vagi also failed to prevent or modify it   The effect of section of the cord is shown in Tracing 3   It would therefore, appear that the rise in pressure in the pulmonary artery is not of nerve origin   A close study of Tracing 4 would certainly give the impression that stasis from the left heart was a factor. as we note in the tracing that the increase in pressure in the pulmonary artery begins during the period of sudden drop in the carotid pressure, exactly what could be expected if stasis were the cause   If we could accept Lowit's explanation that direct transmission of pressure from the left auricle through the pulmonary veins to the pulmonary artery does not necessarily occur, and that increased

pressure in the pulmonary artery is not necessarily transmitted to the pulmonary veins, stasis could still explain this phenomenon

In seeking for an explanation of the rise in the pulmonary arterial pressure without corresponding increase in pressure in the left auricle, it was suggested that capillary thrombosis might be responsible We can readily see that a plugging of the terminal branches of the pulmonary artery would be followed by the above pressure changes Silbermann[17] has shown that capillary thrombosis may be readily induced by various toxic agents, including carbon monoxid and ether, and that the capillaries of the lungs, on account of their exceedingly small caliber and low blood pressure, are especially prone to thrombosis To demonstrate that such thrombosis was antemortem, Silbermann injected 400 to 500 c c of a saturated watery solution of indigo-carmin into a vein of the living animal The areas of tissue in which the capillaries were plugged
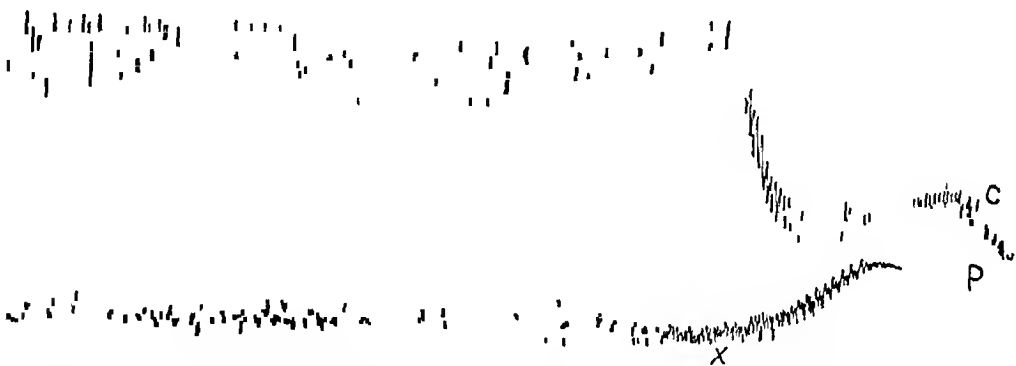
Tracing 4 —Showing the simultaneous changes taking place in the carotid and pulmonary pressure after acetic ether   C, carotid, P, pulmonary artery, X, 0 5 c c acetic ether intravenously

would not be colored, while tissues with patulous vessels would take the stain We resorted to this test in animals that had previously received iodid or acetic ether in sufficient amounts to cause pulmonary edema, but were unable to demonstrate the presence of capillary thrombosis Microscopic examination of sections of the lung also gave negative results

Adrenalin Chlorid —On account of the occasional recurrence of pulmonary edema in rabbits after the intravenous injection of adrenalin chlorid, an attempt was made to study the blood-pressure changes during the development of such an edema With cannulas in the carotid and pulmonary arteries efforts were made to produce a pulmonary edema by intravenous injection of 0 5 to 2 c c of a 1 1,000 solution of adrenalin

17 Silbermann, O   Ueber das Austreten multiples intravitales Blutgerinnungen nach acuter Intoxication durch Chlorsaure Salze-Arsen, Phosphor und einige andre Blutgifte Virchow s Arch f path Anat , 1889, cxvii, 288

chlorid   Although the experiment was repeated on a considerable number of rabbits, we were never able to obtain one in which a pulmonary edema could be produced by this measure   The experiment was then modified by cutting off part of the circulation   The descending portion of the thoracic aorta was ligated, beyond where the large trunks are given off to the head and upper extremities   This ligation was followed by a very marked rise in the carotid pressure, the pressure in the pulmonary artery, however, was not affected, nor did pulmonary edema develop   The animal then received 0 5 c c of a solution of adrenalin chlorid, which caused a still further rise in the carotid pressure in the pulmonary artery, and the development of a marked pulmonary edema   This same experiment was repeated on dogs with similar results   These pressure changes are shown in Table 9 and also in Tracing 5
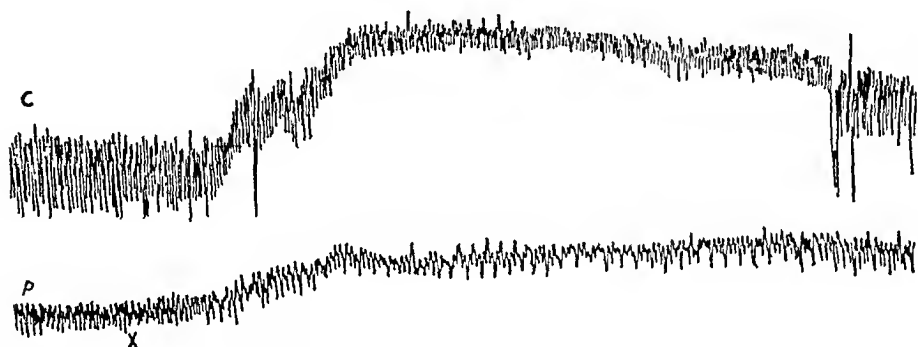
Tracing 5 —Effect of adrenalin after ligation of the thoracic aorta   C, carotid, P, pulmonary artery, X, 1 c c adrenalin chlorid 1 1,000

TABLE 9 —EFFECT OF ADRENALIN AFTER LIGATION OF THE THORACIC AORTA

Time	Carotid Pressure	Pulmonary Arterial Pressure	Remarks
	106	9	Before ligation of aorta
	146	7	After ligation of aorta
30 seconds	210	19	After 1 c c adrenalin chlorid 1 1000
120 seconds	204	18	Animal killed, pulmonary edema

The development of pulmonary edema in these animals can best be explained by the vasoconstrictor action of the adrenalin raising the pressure in the systemic circulation to such a degree that the left ventricle is unable to empty itself completely   Stasis in the left auricle, pulmonary vein and pulmonary artery then follows with a consequent rise in pressure in the pulmonary artery and the development of edema   This is quite in accord with the theory advanced by Meltzer to explain the pulmonary edema following the use of adrenalin   By slow transfusion with a solution of adrenalin chlorid, 1 1 000,000, we were able to maintain a very high carotid pressure for twenty minutes, the pulmonary pressure

also showing a decided rise in case the thoracic artery had been previously constricted Edema under these circumstances is of especial interest, as its development is associated with high pressure in the systemic circulation One of the strongest arguments against the clinical application of Welch's theory is that it did not account for the high tension pulse often seen during an attack In nephritis with extremely high blood pressure, the failure of the left ventricle to empty itself completely, with resulting stasis, increase in pressure in the pulmonary artery, and development of acute pulmonary edema, with high tension pulse, may occur exactly as it does in the rabbit after the use of adrenalin It is well understood that high systolic pressure may be associated with small systolic output provided the pulse pressure, i e, the difference between the systolic and diastolic pressure, is reduced A high-tension pulse does not necessarily imply normal systolic output

Tracing 6 —Effect of bleeding, after artificial mitral stenosis X', 15 c c of blood withdrawn from the jugular 15 c c withdrawn at X" X''' X'''', C, carotid, P, pulmonary

Artificial Mitral Stenosis —The effect on the pulmonary pressure and the development of pulmonary edema was studied in dogs in which an artificial stenosis had been produced With a little practice a ligature may be passed through the auriculoventricular groove in such a manner that on tightening it any degree of mitral stenosis may be produced The first effect of narrowing the orifice is a fall in the carotid pressure This occurs only after a considerable degree of constriction In one animal the orifice was reduced one-half in size with only slight effect on the carotid pressure When the constriction is carried still further, a rise in pressure in the pulmonary artery takes place This rise may be slight or very marked, depending on the degree of obstruction induced Table 10 shows the changes of blood pressure after constriction of the orifice from 8 to 3 mm All of these animals when a satisfactory constriction of the orifice was obtained developed a decided pulmonary edema of the hyperemic type After the constriction had reached a moderate degree, dilatation of the left auricle occurred followed by dilatation of the right auricle and right ventricle The development of edema under these circumstances is best explained by Welch's theory

TABLE 10 —PULMONARY AND CAROTID PRESSURE FOLLOWING MITRAL STENOSIS

Time	Carotid Pressure	Pulmonary Arterial Pressure	Remarks
	100	9	Before production of stenosis
60 seconds	50	9	Slight constriction mitral orifice
300 seconds	84	14	Orifice constricted from 8 to 3 mm
420 seconds	80	18	Showing increase in pulmonary pressure although no change in constriction since previous read ing

EXPERIMENTAL THERAPEUTIC AGENTS

In applying therapeutic agents ꞌto the treatment of experimental edema, it can readily be seen that no single remedy would be indicated in all instances. While the pulmonary arterial pressure was increased in most forms of experimental edema, the systemic blood pressure varied, low in some instances, high, however, in that type produced by adrenalin. Assuming that mechanical factors are important, a drug or method of treatment, in order to be considered beneficial should tend to equalize the work of the cardiac chambers. The only form of experimental edema that yields readily to treatment is that produced by muscarin. Atropin has here a physiologic antagonistic action, and under its use the left ventricle assumes its normal working power, the blood pressure becomes equalized and the edema gradually subsides. Atropin, however, in pulmonary edema from other causes was without beneficial effect. When used in the edema produced by acetic ether or iodids the pressure in both carotid and pulmonary artery was increased, the developing edema was not checked nor was the life of the animal prolonged.

Nitroglycerin was also tried in the edema produced by acetic ether and iodids with the idea that perhaps the rise in pressure in the pulmonary artery was in part due to a vasoconstrictor action. As previously mentioned, however, large doses of nitroglycerin under these circumstances did not reduce the pulmonary arterial pressure. In the edema induced by adrenalin with high systemic pressure, the nitroglycerin was ineffectual on account of its action being interferred with by the more powerful adrenalin. This does not mean, however that in pulmonary edema of this type in man nitroglycerin might not be beneficial. as the high tension in the systemic circulation may be due to other agents than adrenalin, which yield, slightly at least to the vasodilators.

Barium chlorid on account of its constriction of the pulmonary artery, due to its action directly on the unstriated muscle was tried both for the prevention and alleviation of experimental pulmonary edema. As there is hyperemia of the lung with the edema, and the theory has been advanced that pulmonary edema is due to vasomotor paresis of the

pulmonary aitery, it was thought that barium chlorid might exert a desirable influence The results, however, were entirely negative either as iegards preventing the edema or modifying its course Changes in pressure in the carotid and pulmonary artery occuired as in the untreated animals

Digitalis was also tried, both in preventing and alleviating developed edema The only form of edema in which it appeared to have any beneficial action was that due to artificial mitral stenosis Here in conjunction with venesection it contributed to the equalization of the ciiculation

The effect of venesection was noted in animals with acute pulmonary edema fiom the various causes The results on the whole were quite disappointing Before any effect could be seen on the piessuie in the pulmonaiy arteiy, it was necessary to withdraw a sufficient amount of blood to lowei the general blood pressure materially Rapid withdrawal of 10 to 20 c c of blood from the jugular vein of a 12-kilo dog would lower the pressure in the pulmonary artery momentarily, but it would promptly retuin to the previous level (see Curve 5) The withdiawal of 100 c c within two minutes in an 8-kilo dog would cause a permanent fall in both carotid and pulmonary artery, which, however, could not be considered as beneficial When digitalis was given in conjunction with moderate bleeding, in the edema due to mitial stenosis, the pulmonary pressure could be lowered slightly and the carotid pressure raised to its previous level It was not determined whether this increase in pressure in the systemic circulation was due to increased systolic output oi to general vasomotor constiictions, however, as there was a slight fall in piessuie in the pulmonary artery apparently the systolic output of the left ventiicle was somewhat increased With the adienalin edema bettei results were obtained by bleeding from an artery than from a vein

Although our therapeutic results in the treatment of experimental edema weie so unsatisfactory, a knowledge of the factors at work in producing an edema should be of assistance in its intelligent treatment We must remember that many attacks of acute pulmonary edema in man subside without treatment and, for this reason, clinical experience in the value of therapeutic agents must be accepted with considerable reserve Considering marked disturbance of the ciiculation as the chief underlying cause of the trouble, intelligent rather than empirical treatment should be instituted To give adrenalin, digitalis or caffein in a case of edema associated with high arterial tension might hasten a fatal termination Atropin under these conditions, on account of its raising the blood piessuie by quickening the heart action, would not be indicated In this type of edema efforts should be diiected toward loweiing the

arterial tension, by the vasodilators or counter-irritation to the surface of the body or by bleeding with the type of edema associated with low-tension pulse, this form of treatment might be injurious Here digitalis and caffein would be indicated It is interesting to note the frequency with which atropin is recommended in the treatment of acute pulmonary edema The foundation of this treatment is apparently its beneficial results in the edema due to poisoning with toadstools and pilocarpin The pulmonary edema developing in nephrities after the use of pilocarpin is often due in reality to the drug, as it produces edema in the same manner as muscarin, and atropin is the physiologic antidote The second reason for its general use is based on its power to lessen glandular secretion It is unnecessary to state that in acute pulmonary edema we are not dealing with a glandular secretion, but a transudation The use of adrenalin is to be discouraged as being, under certain conditions very dangerous and probably always valueless Oxygen inhalations are harmless and give some temporary relief and may assist in tiding the patient over Morphin, by allaying the patient's fears, is decidedly beneficial in its effects and could be safely used in small doses in any type of acute pulmonary edema Venesection is another measure which is probably safe if practiced on individuals not already decidedly anemic Its real value, however, can only be determined by extensive clinical observations Unfortunately for the science of medicine, no one physician is able to see a sufficient number of cases of acute pulmonary edema during his lifetime to make a careful comparative study of the value of the various forms of treatment

CONCLUSIONS

1 When pulmonary edema develops after exposure to nitric oxid or ammonia, there is no evidence that mechanical factors play a rôle i e we are unable to detect any evidence of disproportion between the working power of the two sides of the heart

2 The acute pulmonary edema following inhalation or intravenous injection of acetic ether is usually associated with evidence of disproportion in the working power of the two sides of the heart, as there is a fall in the systemic and a corresponding rise in pressure in the pulmonary artery When large doses of acetic ether are injected intravenously, pulmonary edema may occur without evidence of disproportion in the working power of the two sides of the heart thus showing that such changes are not essential for its appearance It would appear therefore that mechanical factors are not responsible for the edema

3 In the acute pulmonary edema produced by iodids there is in the beginning a marked rise in pressure in both the systemic and pulmo-

naiy ciiculation, later the systemic blood pressuie falls, but the piessuie in the pulmonary artery iemains high This disproportion in the working power of the two ventiicles was piesent in eveiy instance, it would, therefore, appear fiom our expeiiments that the edema might be explained by mechanical agents, although not necessarily so

4 The intiavenous injection of adrenalin chloiid, when pieceded by ligation of the thoiacic aorta, causes pulmonary edema Appaiently as a iesult of the great increase in the systemic blood pressure after such a piocedure, the left ventricle is unable to empty itself completely, stasis and rise in pressure in the pulmonaiy arteiv follows This is perhaps the mechanism of acute pulmonary edema in nephritics with hypeitension

5 In the mechanical edemas, therapeutic measures to be of value should tend to equalize the work of the cardiac chambers This may mean the use of vasodilators in some instances, in otheis the use of diugs that stimulate the heait activity

100 State Stieet

A COMPARATIVE STUDY OF SERUM DIAGNOSIS IN SYPHILIS *

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Although only three years have elapsed since the Wassermann-Neisser-Bruck reaction for the diagnosis of syphilis was described, it has become in this time a well-established diagnostic method and it, or its modifications, are now in use in all large medical centers During this period, which must be considered as a stage of experimentation and testing, a number of modifications of the original method, and also several practically new methods for serum diagnosis have been devised Several of these have been subjected to critical examination by various investigators, and although from the mass of evidence the original method, with a slight modification, appears to be the most satisfactory, it has seemed to me advisable to carry out a comparative, critical study of the more important modifications The methods selected for study are the following

I Wassermann's original method

II Noguchi's precipitation method for spinal fluids, with a discussion of the precipitation reactions of Porges, Fornet, Klausner and Noguchi for blood serum

III Bauer's simplification of the Wassermann reaction, with a discussion of Tschernogubow's modification

IV Noguchi's complement deviation method

I THE WASSERMANN METHOD

In his adaptation of the Bordet-Gengou phenomenon of complement deviation, Wassermann used as a hemolytic system (a) 1 c c of a 5 per cent suspension of washed red blood cells of the sheep, (b) two units[1] of hemolytic amboceptor made by immunizing rabbits to sheep's red

1 The hemolytic unit is the amount of inactivated hemolytic serum that will completely hemolyze 1 c c of a 5 per cent suspension of sheep's red blood cells in the presence of 0 1 c c of fresh guinea-pig serum as complement

blood cells, and (c) as complement 0 1 c c fresh guinea-pig serum For syphilitic antibody 0 2 c c of serum from suspected patients was selected as the maximum quantity, and for antigen a watery extract of a liver of congenital syphilis known to be rich in *Spirochæta pallida*

At this time Wassermann considered his antigen to be an extract of the specific organism and the fixation of complement to be therefore a true antigen-antibody reaction The subsequent work on the nature of the antigen has, however, destroyed this view Marie and Levaditi,[2] in applying the reaction to the spinal fluid from tabes and general paralysis, found that extracts of livers from non-syphilitic fetuses gave a weak reaction, and such extracts when used in large quantities acted satisfactorily as antigens Weil,[3] using extracts of tumors, obtained positive reactions with syphilitic sera, and from such results he attacked the specificity of the method Such results clearly proved that the so-called antigen was not the *Spirochæta pallida* or its products, and numerous workers took up the study of the nature of this substance Under Wassermann's[4] direction, alcoholic extracts of syphilitic livers were made and found to contain the active substance Similar experiments[5] were repeated with the normal organs of man and the lower animals and all such extracts were found to be potent antigens As extraction by alcohol indicated the substance to be lipoid in nature, different members of the lipoid group, in the pure state, were tested Among these may be mentioned lecithin, cholesterin, the sodium salts of the bile acids, sodium oleate and oleic acid Combinations of these in definite proportions have been suggested for us as antigen, but so far the total extracts of organs seem to act the best, and of these, extracts of syphilitic organs can be used in the smallest quantity

To be satisfactory an antigen should possess the following qualities (1) It should not prevent hemolysis when mixed with the hemolytic system, (2) it should give a positive reaction in a large proportion of syphilitic cases and should not react with non-syphilitic sera; (3) it should retain its antigenic qualities for some time so that comparative tests may be made

The watery extracts are prone to undergo sudden changes, while the alcoholic extracts keep well at room temperature Each antigen must be tested as to the first two qualities before it is finally adopted as a reagent It would be a great advantage if some rule could be formulated for the

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2 Marie, A , and Levaditi, C Ann de l'Inst Pasteur, 1907, xxi, 138
3 Weil, E Wien klin Wchnschr , 1907, xx, 527
4 Wassermann, A Berl klin Wchnschr , 1907, xliv, 1599
5 Porges, O , and Meier, G Berl klin Wchnschr , 1908, xlv, 731

making of antigen, but as yet no definite antigen has been generally adopted In many places alcoholic extracts of animal organs are used and Wassermann[6] lately admits that such antigens may be employed provided they have been previously compared with a known antigen He, however, prefers the watery extract for doubtful or weak sera

In the first hundred tests by the Wassermann method in this report (see Tables 3 to 9) the antigen was a 0 1 per cent emulsion of lecithin furnished by Dr Noguchi of the Rockefeller Institute, in the later cases an alcoholic extract of dog's liver was used and found to work in a satisfactory manner This has been lately compared in about one hundred tests with an alcoholic extract of syphilitic liver and the latter has been found to give somewhat more marked reactions with weak sera

On account of the small amount of blood obtained by puncture of the ear, hardly sufficient for the numerous controls necessary, I have found it advisable to reduce the quantities of serum and complement by one-half that recommended in the original method, that is, to use 0 1 c c of the patient's serum and 0 05 c c of guinea-pig's serum to each tube The other factors were reduced in the same proportion Some investigators have used the drop method to economize serum, but I thought it better to reduce all the reagents in a definite proportion

II PRECIPITATION METHODS

The complicated nature of the Wassermann reaction has led to many attempts to simplify the serum diagnosis of syphilis Various precipitation methods have been devised, but found not to be specific Among them may be mentioned the Porges[7] reaction with lecithin, the Fornet[8] reaction, by mixing serum from florid syphilis with that from parasyphilis, and the Klausner[9] reaction, which demonstrated an increase in globulin by mixing suspected sera with distilled water Noguchi[10] demonstrated an increase in globulins by precipitating these bodies with a one-half saturated solution of ammonium sulphate, centrifuging, pouring off the supernatant fluid, redissolving them in normal salt solution, and adding 10 per cent butyric acid A flocculent precipitate in two hours was considered evidence of a decided increase in the globulin fraction While this increase of globulin is often found in syphilis it is not pathognomonic, for it is present in many other infectious diseases, and earlier

6 Wassermann A Deutsch med Wchnschr, 1909, xxxv, 418
7 Porges, O Wien klin Wchnschr, 1908, xxi, 206
8 Fornet and Schereschewsky Munchen med Wchnschr, 1907 liv, 1471
9 Klausner, E Wien klin Wchnschr, 1908 xxi, 214
10 Noguchi, H Jour Exper Med, 1909, xi, 84

expeimental work has shown that the formation of immune bodies, both to bacteria and other oiganic substances, frequently is accompanied by an increase in globulin Noguchi himself has called attention to the fact that the increase is found in many othei conditions

Noguchi[10] also devised a precipitation method for detecting an increase of the protein of the spinal fluid in parasyphilitic diseases By boiling 0 1 c c of the fluid with 0 5 c c of a 10 per cent butyric acid solution and adding 0 1 c c of normal sodium hydroxid solution, and again boiling, a gianular precipitate is obtained This reaction he at first consideied diagnostic, but latei found it in othei forms of meningitis Gay and Fitzgeiald[11] confirmed Noguchi's findings in tabes and geneial paralysis, but obtained the same ieaction in meningitis, and some psychopathic conditions In applying this test to spinal fluids, I obtained the reaction in three cases of tuberculous meningitis, two of gastro-enteritis with symptoms of meningeal irritation, one of alcoholic cerebral edema, and one of pneumonia The spinal fluid from a case of congenital syphilis and that from an autopsy of a man with visceral syphilis also gave the granular precipitate The non-specificity of the reaction prevents its use as a diagnostic measure, although it may be applied in cases of known syphilis to determine if the syphilitic process is active in the centiaI nervous system

III BAUER'S MODIFICATION OF WASSERMANN'S METHOD

The failuie of the various precipitation ieactions as reliable diagnostic measures forces us to fall back on the complement deviation method Vaiious attempts have been made to simplify the original process It was noted that frequently the tubes under trial showed hemolysis befoie the control tube without serum, and such observations led to the discoveiy that many sera possessed the powei of hemolyzing sheep cells without the addition of the hemolytic seium from an immunized iabbit Taking advantage of this, Bauer[12] omitted the addition of foieign hemolytic serum In other iespects his procedure is practically that of the original method He mixes the suspected serum with complement and antigen, incubates to bind complement, and then adds only sheep cells and again incubates As a control he uses the seium from a non-syphilitic peison His protocol would read thus

11 Gay, F P , and Fitzgerald, J G   Boston Med and Suig Jour , 1909, clx, 157

12 Bauei, J   Deutsch med Wchnschr , 1908 xxxiv, 698

PROTOCOL I —BAUER METHOD

	Test for Diagnosis	Control Set with Normal Serum
Control tubes without Antigen	**Tube 2** a Patient's serum containing hemolysin (and syphilitic antibody?)	**Tube 4** a Normal serum containing hemolysin
	b Complement	b Complement
Determinative tubes with Antigen	**Tube 1** a Patient's serum containing hemolysin (and syphilitic antibody?)	**Tube 3** a Normal serum containing hemolysin
	b Complement	b Complement
	c Antigen	c Antigen

Incubation at 37 C for 1 hour
Washed sheep's red blood cells
Incubation at 37 C for 2 hours   Then in ice box over night

If hemolysis is inhibited in Tube 1 the reaction is positive This method has been adopted in a few clinics in Germany Bering[13] reports that the method gives as good results as the original Wassermann method and prefers it because it is simpler and requires less of the patient's serum Hinrichs[14] finds it more satisfactory and reports the results as given in Table 1

TABLE 1 —HINRICH'S COMPARISON OF BAUER AND WASSERMANN METHOD

Type of Syphilis	Bauer Method % Positive	Wassermann Method % Positive
Untreated	100	100
Fairly well treated	70	40
History of over four years, little treated	87	65
History of over four years, well treated	66	50

Meirowsky[15] did not find it so reliable and obtained a higher per cent of positive results in the Wassermann reaction Noguchi reports having tried the method in over a hundred cases and says that it is unreliable because of the inconstant content of anti-sheep amboceptor

I have compared this method with those of Wassermann and Noguchi in sixty-five cases of syphilis and thirty-two non-syphilitic individuals The results with the syphilitic sera are given in Table 2 The control sera, all negative with the Wassermann method, showed complete hemolysis in eleven cases, partial in thirteen, slight in three and none in five The control tubes with the syphilitic sera showed complete hemolysis in twenty-six cases and insufficient or no hemolysis in thirty-nine The whole number shows 37 sera, or 38 per cent, with sufficient anti-sheep amboceptor to perform the test, and 60 sera, or 62 per cent, with an insufficient amount Of the cases of syphilis, 65 per cent reacted posi-

13 Bering, F   München med Wchnschr, 1908, lv, 2476
14 Hinrichs   Med Klinik, 1908, iv, 1349
15. Meirowsky, E   Berl klin Wchnschr, 1909, xlvi, 152

TABLE 2 —COMPARISON OF WASSERMANN, NOGUCHI AND BAUER REACTIONS *

No	Wasser-mann	Noguchi	Amount of Hemolysis in Test Tube	Amount of Hemolysis in Control Tube	Amount of Hemolysin	Result
			PRIMARY SYPHILIS			
190	++	++	None	Nearly Complete	Sufficient	++
245	++	++	None	Complete	Sufficient	++
492	+	+	None	Complete	Sufficient	++
			SECONDARY SYPHILIS			
192	++	+—	None	Partial	Insufficient	+?
196	++	++	None	None	Insufficient	?
218	++	++	None	Partial	Insufficient	+?
236	++	++	None	Complete	Sufficient	++
241	—	—	None	Complete	Sufficient	++
257	++	++	None	Complete	Sufficient	++
499	+	+	None	Complete	Sufficient	++
			TERTIARY SYPHILIS			
171	—	+	Slight	Complete	Sufficient	+
173	++	++	None	Nearly Complete	Sufficient	+
204	++	+	None	None	Insufficient	?
220	++	+	None	Complete	Sufficient	++
221	++	+	None	Slight	Insufficient	+?
235	++	++	None	Slight	Insufficient	+?
256	++	++	None	Partial	Insufficient	+?
537	++	++	None	Complete	Sufficient	++
			LATENT SYPHILIS			
184	+	+—	Partial	Partial	Insufficient	?
213	+	+	None	Complete	Sufficient	++
222	+—	—	Partial	Partial	Insufficient	?
223	—	—	None	None	Insufficient	?
224	—	+—	Partial	Partial	Insufficient	?
243	—	—	None	None	Insufficient	?
244	—	—	None	None	Insufficient	?
246	+	++	Slight	Partial	Insufficient	?
249	—	+	Partial	Partial	Insufficient	?
254	—	+	None	None	Insufficient	+
489	+—	+	Slight	Complete	Sufficient	++
494	—	+	None	Complete	Sufficient	?
514	—	—	Partial	Partial	Insufficient	?
518	+—	+—	Slight	Slight	Insufficient	?
534	—	—	Complete	Complete	Sufficient	—
536	++	++	None	None	Insufficient	?
			VISCERAL SYPHILIS			
178	+—	+—	Partial	Partial	Insufficient	?
181	++	++	None	Nearly Complete	Sufficient	++
182	—	—	None	None	Insufficient	?
187	+	+—	None	Partial	Insufficient	+?
188	+	—	Slight	Slight	Insufficient	?
193	—	—	Slight	Slight	Insufficient	?
195	+	+—	Slight	Complete	Sufficient	+
202	—	—	Complete	Complete	Sufficient	—
211	—	—	Parital	Partial	Insufficient	?
215	—	—	Complete	Complete	Sufficient	—
219	++	++	None	None	Insufficient	?
226	+—	+	None	Slight	Insufficient	+?
227	++	++	None	Slight	Insufficient	+?
229	—	—	None	None	Insufficient	?
247	—	+	Complete	Complete	Sufficient	+
503	—	—	Slight	Complete	Sufficient	+—
504	—	—	Partial	Complete	Sufficient.	+—
508	+—	+	Slight	Complete	Sufficient	+
510			Slight	Complete	Sufficient	
			CONGENITAL SYPHILIS			
225	++	+	None	Slight	Insufficient	+?
237	++	++	None	Slight	Insufficient	+?
			TABES			
183	—	—	None	Slight	Insufficient	+?
186	+	+	None	Partial	Insufficient	+?
189	+	+	Complete	Complete	Sufficient	—?
210	—	—	None	Slight	Insufficient	+?
212	—	—	Partial	Partial	Insufficient	?
250	+—	++	Partial	Partial	Insufficient	?
509	+—	+	None	None	Insufficient	?
517	++	++	None	Complete	Sufficient	++
532	—	—	Complete	Complete	Sufficient	—
535	++	++	None	None	Insufficient	?

* ++=Complete Inhibition
+—=Marked Inhibition
+ —=Slight Inhibition
—=Complete Hemolysis

tively with the Wassermann and 67 per cent with the Noguchi method The Bauer method gave 33 per cent positive, 20 per cent doubtful-positive, 9 per cent negative and 38 per cent in which a diagnosis could not be made   Five spinal fluids were similarly tested and none was found to contain anti-sheep amboceptor   Bauer in his original communication says that the blood of suckling infants can not be used and recommends that a little serum from a normal adult be added to that of infants   It would seem better to add a known quantity of foreign hemolytic serum so that the results could be more accurately measured

The cause of the variation in the amount of anti-sheep amboceptor has not been explained   The thought naturally occurs that perhaps the eating of mutton excites the formation of this body and that the variations in the results from different cities may be due to the fact that this meat is used more in some places than others   Some ground for this supposition is afforded by the work of Rosenau and Anderson[16] on hypersusceptibility and immunity   They have shown that guinea-pigs may be sensitized to horse and cattle serum by feeding them horse-meat or beef uncooked   We have no evidence however that the results of those experiments may be applied to man

The fact that some samples of sera are rich in anti-sheep amboceptor explains also the negative Wassermann reactions in certain cases of evident syphilis   Morgenroth and Sachs[17] have shown that with a fixed quantity of cells, complete hemolysis will take place by varying the amount of complement and amboceptor inversely to one another   They found that with 1 c c of a 5 per cent suspension of sheep's red blood cells and 0 1 c c of guinea-pig serum as complement, that 0 05 c c of rabbit's serum as amboceptor produced complete hemolysis, if 0 2 c c or 0 4 c c of the same rabbit's serum was used only 0 01 c c or one-tenth the amount of complement was required   Other experiments showed that a fourfold increase of amboceptor caused such a change that only one-twentieth the amount of complement was needed   From this it can be readily seen that if a large hemolytic amboceptor content were present with a small syphilitic antibody content so that not quite all the complement was absorbed, the reaction might be negative   Noguchi[18] reports finding as high as twenty units of anti-sheep amboceptor in some samples of human serum   He also found that four units of amboceptor prevents the detection of one unit of syphilitic antibody   *On account of*

16 Rosenau M J and Anderson, J F   Bull No 36 Hyg Lab U S P H and M-H S, Washington 61
17 Morgenroth J and Sachs, H   Berl klin Wchnschr, 1902, xxxix, 817
18 Noguchi H   Jour Exper Med, 1909, xi, 392

these observations, if a specimen of blood under examination produces rapid hemolysis, it is well to determine the amount of antibody present At times this will be the exact amount necessary for Bauer's modification Case 241 under secondary syphilis (Table 3) shows this very well In this patient the Wassermann was negative, but the Bauer positive This serum was from a man who had become infected four months previously, had ten weeks' treatment, and presented only lesions of the soft palate At other times the hemolytic content may be so high that the dilution required to obtain only two units of amboceptor would completely prevent the detection of a small amount of syphilitic antibody Such a case is that of a woman who eight years ago was infected with syphilis, at which time she had a short course of treatment She then disappeared from observation until eight months ago, when she returned to the hospital with tertiary lesions of the skin Treatment caused these to disappear, but two months ago she began to have shooting pains in the legs and vesical symptoms Examination revealed the Argyll-Robertson pupil, Romberg's sign, and some incoordination in the movement of the legs The case is undoubtedly one of beginning tabes with syphilis as an etiologic factor Treatment had been inefficient, but the serum reaction was negative with both the Wassermann and Bauer tests, but positive by Noguchi's method Investigation showed that the amount of serum used contained five units of anti-sheep amboceptor, enough to mask the weak syphilitic antibody that would be expected I have frequently noted that the tubes in cases of known syphilis which give a negative Wassermann reaction are the first to hemolyze, and am sure that this explains a number of negative reactions

Meirowsky[15] says that he makes it a rule to repeat the reaction, substituting the Bauer technic for the original method, when the serum from a case strongly suspicious of syphilis fails to give the reaction As a routine it might be well to introduce a control tube with one-half the amount of serum usually employed in the Wassermann test, if this, with 0 1 c c of complement, should produce complete hemolysis of the usual number of cells, it would give a clue to the cause of negative findings with certain sera, and would justify repeating the reaction with Bauer's modification

Tschernogubow[19] described a method whereby the complement and cells present in human blood were utilized in a complemental deviation test He diluted 0 4 c c of blood to 4 c c with normal salt solution and used 1 c c in each of four tubes His source for antihuman amboceptor is not stated Protocol 2 gives his method

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19 Tschernogubow, N Berl klin Wchnschr, 1908, xlv, 2107

PROTOCOL II —Tschernogubow Method

Control Without Antigen or Hemolytic Amboceptor	Control Without Antigen
Tube 2	**Tube 1**
a Blood dilution containing complement and cells	a Blood dilution containing complement and cells
Tube 3 **Determinative Tube**	**Tube 4** **Control Without Hemolytic Amboceptor**
a Blood dilution containing complement and cells	a Blood dilution containing complement and cells
b Antigen	b Antigen

Incubation at 37 C for 1 hour
Add hemolytic amboceptor to 1 and 3
Incubation at 37 C for 2 hours

Tube 1 shows hemolysis, Tube 2 shows no hemolysis, Tube 3 (test) will show no hemolysis if disease is syphilis, Tube 4, to show that antigen is not hemolytic, should show no hemolysis

While this method appears simple, it does not stand critical analysis Noguchi[20] has studied it and found it impractical for the following reasons

1. Human complement requires for complete hemolysis ten times as much amboceptor as an equivalent amount of guinea-pig complement

2 Human complement is less sensitive to fixation than that of guinea-pigs

3 The quantity of human complement varies greatly, from one to three, with different samples of sera If it were present in excess it would destroy a positive reaction, hence to be accurate each serum would have to be titrated for complement content before applying the test. Dilution would vary the amount of cells present which, aside from the labor involved, would destroy the value of the reaction.

4 If human complement is used there is no way of telling if antigen alone is antihemolytic

5 Old samples of blood could not be used because complement rapidly deteriorates, and the cells undergo spontaneous hemolysis after a time so that controls could not be kept from day to day

Boas[21] condemns the method because active serum is employed

IV NOGUCHI COMPLEMENT DEVIATION METHOD

Noguchi has devised a plan of using an anti-human hemolytic system In his recently published results[18] he presents a large series of observations from which it appears that his method is more delicate than the original Wassermann Instead of the hemolytic series being sheep's cells and hemolytic serum from rabbits, he uses human red blood cells, with anti-human serum from rabbits In this way he hopes to eliminate the

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20 Noguchi, H   Proc Soc Exper Med and Biol , 1909, vi, 77
21 Boas, H   Berl klin Wchnschr , 1909, xlii, 400

great variability in the amount of hemolytic amboceptor present in a given serum   In other respects the method is one of complement deviation in which the five factors used are separate, can be accurately measured, and any of them tested, should this be necessary, to control the work   The cells used are in the proportion of one drop of blood to four cubic centimeters of normal salt solution   They are not washed, but well shaken to insure a uniform emulsion [22]   One cubic centimeter of emulsion is used in each tube and this is added before the first incubation   The serum to be tested is employed in the amount of one drop from a capillary pipette   At times two drops may be used, but as this amount is often found to be antihemolytic, Noguchi recommends one drop   This serum is not inactivated   As complement 0 04 c c of fresh guinea-pig serum is employed, as hemolytic amboceptor, two units of the serum of a rabbit immunized to human red blood cells   The titer of such serum must be over 0 01 c c for one unit   As antigen 0 3 per cent solution of impure lecithin in equal parts of absolute alcohol and normal salt solution, or alcoholic extract of syphilitic livers, one drop from a capillary pipette, is used   In making this test I have followed the Noguchi protocol, with two added controls (Tubes 7 and 8)

PROTOCOL III —NOGUCHI METHOD

	Test for Diagnosis	First Control Set Known Syphilitic Serum	Second Control Set Known Non-Syphilitic Serum	Third Control Set Without Serum
				Tube 8
Control tube without Antigen for each test	Tube 2 a Patient's serum	Tube 4 a Positive serum	Tube 6 a Normal serum	
	b Human blood suspension	b Human blood suspension	b Human blood suspension	b Human blood suspension
	c Complement	c Complement	c Complement	c Complement.
				Tube 7
Determinative tubes containing Antigen	Tube 1 a Patient's serum	Tube 3 a Positive serum	Tube 5 a Normal serum	
	b Human blood suspension	b Human blood suspension	b Human blood suspension	b Human blood suspension
	c Complement	c Complement	c Complement	c Complement
	d Antigen	d Antigen	d Antigen	d Antigen

Incubation at 37 C for 1 hour *
Antihuman hemolytic amboceptor to all tubes
Incubation at 37 C for 2 hours   Let stand at room temperature over night

* For incubation a water-bath was used instead of a thermostat   This insures a more constant temperature of the surrounding medium, and brings the solution to the required temperature sooner

Tubes 2, 4, 6, 8, 5 and 7 should be hemolyzed   No hemolysis should be seen in 3, and if the case is syphilitic, Tube 1 should show the same

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22 Noguchi now advises that the cells be washed by allowing the emulsion to stand over night, pouring off the clear supernatant solution and adding fresh salt solution up to the original volume   (Personal communication)

inhibition   It can readily be seen that this method is much simpler than the Wassermann technic   The cells are always easily obtained in the quantities needed and no centrifuge is necessary to wash them   Inactivation of the serum is not required, as the complement in the serum, as well as any mixed with the cells, is supposed to be absorbed during the first incubation period

In order to render the method more available to persons without the facilities of organized laboratories, Noguchi prepared the different reagents by impregnating filter paper with amboceptor, complement and antigen in the proper quantities   He has shown[23] that complements and opsonins when dried at 23 C retain their activity for a long time, and even withstand heating to 100 C   Immune bodies are even more resistant to the effects of desiccation   Where guinea-pigs are not readily obtained he recommended the use of dried complement, but suggested that when this serum could be obtained fresh it would be better to use it in the strength of 0 04 c c

This simplification renders the method very attractive, but before it can be accepted it must be thoroughly tried, and controlled by a method which has gained the most universal acceptance, such as the Wassermann technic

A question which comes up in connection with Noguchi's method is that of isohemolysins   The work which has been done lately in hemolysis in cancer has called attention to the presence of isohemolysins in the blood in a number of diseases   Eisenberg[24] has demonstrated isohemolysins in five out of eight cases of syphilis   Weil[25] found hemolysis of alien cells in one out of two cases of lues   The proportion of cells and serum in such experiments is different from that used in the serum diagnosis test, and no foreign complement is added in the cancer test, but the presence of isohemolysins must be considered and might mask certain weakly positive reactions just as the existence of anti-sheep amboceptor masks the complement absorption in certain of the Wassermann reactions   Noguchi has suggested that the tubes be carefully observed for evidence of hemolysis at the end of the first incubation period, and if this is found, the case might be considered one of malignant disease   This has been done in all my tests with evidence of such hemolysis only three times   It has been noted however, that a few of the cases of carcinoma showed quite rapid hemolysis after the hemolytic

23 Noguchi H   Jour Exper Med , 1907 ix, 462
24 Eisenberg   Quoted by Weil   Jour Med Research, 1908, xix, 281
25 Weil R   Jour Med Research, 1908, xix, 281

amboceptor had been added, such hemolysis taking place before that in the control tubes Occasionally this phenomenon has been noted in the tubes containing serum from syphilitic patients which gave a positive Wassermann reaction This masking of the syphilitic antibody explains the failure to obtain positive results in a small percentage of the syphilitic sera In such cases, with the method of collecting the patients blood, it was impossible to repeat the test accurately with the patient's own cells, but it would seem wise in practice always to use the patient's own cells in applying this reaction This would necessitate multiplying controls, but for the sake of accuracy such a method should be adopted

The two factors, antigen and amboceptor, dried on paper have differed in the time they can be kept The antigen has been found to be somewhat unstable The first lot furnished me, which at the beginning was perfectly satisfactory, at the end of five weeks gave no reaction with strong luetic serum When, however, two pieces of such samples were used good results were obtained This shows that in one month the antigen in this form had lost one-half its potency, although it was kept in the dark in a tighly stoppered bottle A second lot of material retained its power for a longer time, but at the end of two months failed to react with weak sera This variability in the strength of dried antigen suggests the advisability of keeping in stock an alcoholic solution and preparing the papers frequently, or of using the liquid in definite measured quantities The hemolytic amboceptor, on the other hand, has retained its power in dried form for at least three months Samples made three months ago and kept in stoppered dark-colored bottles still contain two units and react in a perfectly satisfactory manner

In my study of the Noguchi reaction, hemolytic amboceptor prepared on filter-paper by the originator of the method has been used Antigen prepared in a similar manner was used in the first 400 cases but on account of the variability of this form, an alcoholic extract of syphilitic liver has lately been substituted

All material, except complement and syphilitic liver extract, has been obtained from the originator of the method, who desired to see if such material would prove as satisfactory in other hands as in his experience

In nearly all of the tests I have used my own blood for red blood cells in order to have that factor as nearly constant as possible In about fifty cases parallel controls with the patient's blood as indicator have been run, and in no case did I find any difference in the results

The result of the comparison of the Wassermann and Noguchi methods are given in Tables 3 to 9 inclusive

TABLE 3—WASSERMANN AND NOGUCHI REACTIONS IN PRIMARY, SECONDARY, AND TERTIARY SYPHILIS

PRIMARY SYPHILIS

No	Time Since Appearance of First Symptoms	Present Manifestations	Treatment	Wassermann	Noguchi	Remarks
18	Five weeks	Ulcerated chancre, adenopathy	None	++	++	
68	Two weeks	Chancre, inguinal adenopathy	None	+++	+++	
70	Seven weeks	Chancre, adenopathy	None	++	++	
98	Eight weeks	Chancre, inguinal adenopathy	None	+	+	
152	Not stated	"Indurated ulcer," adenopathy	None			
153	Two weeks	Chancre, adenopathy	None	+	+	
210	One week	Mixed sore, adenopathy	None	+	+	
215	Three weeks	Chancre, adenopathy	None	++	++	Developed roseola three weeks later
100	Two weeks	Chancre, adenopathy	None			
558	Four weeks	Chancre, adenopathy	None	+	+	Repeated after two weeks injection, same result
307	Two weeks	"Indurated ulcer," adenopathy	None	+++	+++	
157	Two weeks	Chancre, adenopathy, alopecia	None	+++	+++	
160	Eleven weeks	Chancre, inguinal adenopathy	None	+++	+++	
195	Not known	Chancre, inguinal adenopathy	None			
156	Two weeks	Chancre, adenopathy	None	+	+	Same as case 456, taken one week later
162	Three weeks	Chancre, adenopathy	None	+	+	

SECONDARY SYPHILIS

No	Time Since Appearance of First Symptoms	Present Manifestations	Treatment	Wassermann	Noguchi	Remarks
1	Two months	Roseola	Six inunctions	+++	+++	
5	Three months	Roseola	Twelve inunctions	+++	+++	
13	Not known	Maculopapular	None	+++	+++	
17	Eighteen months	Nodular syphilide of face	Six weeks, pills	+	+	
73	Six months	Papular	Three months, pills	+++	+++	
11	Five weeks	Roseola	One injection, Hg biniodid	+++	+++	
37	Two months	Roseola	One injection, Hg biniodid	+++	+++	
17	One year	Condylomata of anus	Three months, irregular	+++	+++	
18	Two months	Roseola	None			
19	Not known	Roseola	None	+++	+++	
76	Ten months	Papular	Three months, protoiodid pills	+++	+++	
54	Not known	Miliary papular	Six inunctions	++	++	
81	Five weeks?	Roseola	None	+++	+++	
67	Five weeks	Condylomata of anus	Four months	+++	+++	
70	Six months	Syphilide of tongue	None			
59	Not known	Roseola	Nine injections, Hg biniodid	+++	+++	
101	Four months	Roseola	Six weeks, bichlorid pills	+++	+++	
106	Three months	Maculopapular, iritis	None	+++	+++	
107	Five months	Maculopapular	Three months, pills	+++	+++	
109	Three months	Not stated	Eighteen inunctions	+	+	
111	Six weeks	Papular, iritis	None	++	++	
115	Five months	Roseola	Four months	+	+	
112	Denied	Iritis	None			
110	Three years	Condylomata of anus	Two months	+	+	
111	Six weeks	Not stated	None	+	+	
142	One year	Roseola	Six months, none for six months	+	+	
166	Three weeks	Papular	None	+	+	
		Roseola		+	+	

No	Time Since Appearance of first Symptoms	Present Manifestations	Treatment	Wassermann	Noguchi	Remarks
168	Not known	Roseola	None	+++	++	Roseola masked by scabies
150	Not known	Roseola	None	+++	++	
102	One year	Syphilid of tongue	Ten months	++	+++	
196	Three months	Rash, jaundice, aortic diastolic murmur	"Little"	+?	++	
201	Two years	Conjunctivitis	"Fair"	++	++	Repeated after six mos. injections, Wassermann +, Noguchi ++
213	Two months	Chancre of lip, papular eruption	Three injections, Hg salicylate	++	++	
236	Denied	Papular	None	+−	+−	Bauer reaction, ++
211	Four months	Mucous patches in mouth	Ten weeks, pills	++	++	Primary lesion, ++, probably herpetic
257	Two months	Roseola, herpes progenitalis	One injection, Hg salicylate	++	++	
200	Four months	Not stated	Six weeks	++	+++	Cannot tolerate mercury
201	Six months	Papular, iritis	Poorly	+++	+++	
260	Three years	Papular	Poorly	+++	+++	
297	Six months	Iritis	None	+++	+++	
223	Two months	Papular	Four months	+++	+++	
225	Three months	Maculopapular	Five weeks	+++	+++	
326	Three weeks	Not stated	None	+++	+++	
330	Nine years?	Chancre of lip, maculopapular	None	+++	+++	
331	Four months	Papular	Poorly	+++	+++	
335	Five months	Mucous patches in mouth	Six weeks	+++	+++	
316	Three months	Papular	Two weeks	+++	+++	
319	Three months	Roseola	None	+++	+++	
353	Three months	Roseola	None	+++	+++	
354	Two months	Papular	None	+++	+++	
356	Three months	Roseola	None	+++	+++	
379	Six weeks	Maculopapular	Two weeks	+++	+++	
382	Six weeks	Roseola	Two weeks	+++	+++	
400	Five months	"Ill defined eruption"	One injection, Hg salicylate	+++	+++	Had marked scabies mixed with other eruption
101	Three months	Roseola	Little	++	++	
112	Four months	"Rash" nephritis	Little	+?	+?	
118	Eight months	Papulopustular of face	Two months	+++	++	
121	Three weeks	Roseola	None	+++	+++	
126	Three months	Maculopapular	Two weeks, protoiodid pills	+++	+++	
112	One month	Roseola	"Little"	+++	+++	
133	Two months	Maculopapular	One week	+++	++	
151	Two months	Roseola	One week	+++	+++	
160	Six weeks	Roseola	Three weeks, protoiodid pills	+++	+++	
187	Not known	Roseola, angina	None	+++	+++	
188	Not known	Papular, chancre of finger?	None	+−	+−	
106	Denied	Papular	None	++	++	
107	Denied	Papular	Little	+++	++	
190	Denied	Keratitis, myositis	None	+++	++	
523	Denied	Squamous lesions of palms, mucous patches	None	+?	+?	
525	Three weeks?	Papular	One week, mixed	+?	++	Bauer ++.
526	Two and one half years	Papular	One year, mixed	+++	+++	
527	Two years	Nodular	Eight months, pills	+++	+++	No treatment for past year
528	Eight months	Papular	One month	+++	+++	
531	Two months	Papular	Two weeks, protoiodid pills	+++	+++	

TERTIARY SYPHILIS

No	Time Since Appearance of First Symptoms	Present Manifestations	Treatment	Wassermann	Noguchi	Remarks
8	Two and one half years	Serpiginous	Two and one half years	++	++	Very resistant to treatment
12	Thirty years	Gumma of leg	Six months, irregular	++	++	
20	Not known	Gumma of face	Irregular	++	+++	
15	Not known	Gumma of lip	Fair	++	+++	
75	Four years	Serpiginous	Poorly	−|	−−|	Patient very alcoholic
77	"Several years"	Serpiginous	Irregular	++	+++	
82	Nine years	Gummata of legs	Poorly			
85	Forty eight years	Leucoplakia of tongue	Full			Has epithelioma developing on leucoplakia
80	Denied	Serpiginous	None	−|	+|−−	
102	Denied	Syphilitic glossitis	None		++	
111	Not known	Serpiginous	Five weeks, mixed			
116	Fourteen years	Gummata of legs	Irregular	−−−	+−|	Bauer +
101	Fourteen months	Serpiginous	Fourteen months	++	++	
105	Not known	Serpiginous	Poorly	+|	+−|	
171	Not known	Squamous lesion of sole of foot	None	+++	−+++	
184	Fifteen years	Serpiginous	About four years in all	+++	+++	
201	Seven years	Gummata of palate	Poorly	+++	+++	
220	Fifteen months	Gummata of legs	Seven weeks	+++	+++	
221	Thirty five years	Not stated	Irregular	+++	++	
216	Twenty years	Serpiginous	Little	+|	+|	
270	Four years	Serpiginous	Little	+++	−++	
204	Eight years	Gumma of neck	Eighteen months intermittent			
201	Not known	Gumma of penis	Three weeks	++	++	Did not respond to mixed treatment but healed under local applications
721	Three years		Three months, mixed	−|	+|	
128	Two years	Gummata of penis and legs	Irregular	+++	+|	
120	Two and one half years	Gummata of scalp	Two years, continuous	+|	+−|	
115	One year	Syphilitic glossitis	One year, continuous	+|	+|	
152	Four years	Gumma of testicle serpiginous of leg	Six months	+|	+−|	
107	Four years	Syphilid of tongue	Four months	++	++	
674	Denied	Gummata	None	+++	+++	
89	Twenty eight years	Serpiginous	Six months	+++	+++	
102	Four years	Gummata of legs	Three months, irregular	+++	+++	
101	Four years	Serpiginous	Six months	+++	+++	No treatment for three years
127	Three years	Gumma of foot	Intermittent, poorly	+++	+++	Has had three relapses
155	Six months?	Not stated	Little	+++	+++	
150	Denied	Gumma of leg	Four months, intermittent	+++	+++	
Denied	Gumma of palate	None	+++	+++	
Denied	Gumma of leg, edema of foot	None	+++	+++	No treatment for three years
Denied	Gummata of forehead	One year, KI	+++	+++	
170	Fifteen years	Scaling lesions	Three weeks mixed	+++	+++	
181	Denied	Serpiginous	Three months in all	+++	+++	
520	Sixteen years	Serpiginous and gumma	None	+++	+++	No treatment for three years
Four years	Gumma of foot	Five months' injection, Hg salicylate	+++	+++	
757	Eight years	Interstitial glossitis	One year mixed About six months	+++	+++	No treatment for seven years

LATENT SYPHILIS

No	Time Since Infection	Treatment	Wassermann	Noguchi	Remarks
133	One year	None	++	++	Mother of child with congenital syphilis
231	Not known	None		+−	Now has alcoholic neuritis
216	One year	None	++	++	Has typical syphilitic scars and perforation of palate
370	Denied	None	−	−	
7	Two years	Nine weeks, mixed	−+	++	Had squamous syphilid of palm which has disappeared under treatment
25	Six months	Ten weeks	+−	+−	
11	Denied	Eight weeks			
54	Six months	Six months	++	+−	One month later developed frontal periostitis
60	Four months	Three months injection, Hg salicylate			
87	Three years	Eleven months, irregular	++	++	Autopsy later showed tuberculosis, patient gave history of syphilis
95	Several years	Little	++	++	
132	Twenty five years	Six months at beginning of disease	−	−	
136	Not known	Three months, mixed	+	+	Had gumma of arm three months ago
151	Four months	Thirty six inunctions	+−	+−	
160	Not stated	Six months	+−	+−	
222	Eleven months	Five months	+−	+−	
213	Eight months	Little	−	−	
214	Denied	Three months, mixed	−	−	
259	Six months	Five injections, Hg salicylate	++	++	Had squamous syphilid of palm which has disappeared under treatment
337	Seven months	Six months	+−	+−	
318	Ten years	Thirteen injections			
368	Eighteen months	Little	++	++	Has headaches at night, is very neurotic
388	Twelve years	Little			
407	Twelve years	Not known, little	−+	−	
416	Fifteen months	Fifteen injections, Hg salicylate Ten months, protoiodid pills			

No	Time Since Infection	Treatment	Wassermann	Noguchi	Remarks
424	Twenty years	Sixteen months, mixed	·	++	Miscarriage with syphilitic fetus twenty years ago Had syphilitic periostitis two months ago Had syphilitic periostitis two months ago
436	Five months	Sixteen injections, Hg salicylate	−	−	
448	Three months	Seven injections, Hg salicylate	+	++	
455	Four months	Two months, protoiodid pills	+−	+−	Had gumma of leg five months ago
173	Denied	Three months, mixed	++	+	
477	Fourteen months	One year, protoiodid pills	++	++	
480	Denied	Little	+−	++	Bauer ++
404	One year	Seven months, protoiodid pills	++	++	Bauer ++
495	Eight months	Four months, mixed	+−	++	Had positive Wassermann four months ago
514	Five months	Seven months, bichlorid pills	−	−	
521	Nine months	Fourteen injections, Hg salicylate	++	++	Had gumma of elbow eight months ago
522	Forty years	Seven months, "pills"	++	++	
520	Six months	Eight months, mixed	+−	+	
531	Twenty years	Six injections, Hg salicylate; Four months, protoiodid pills	−	+−	Bauer −
23	Eighteen months	"Little"	−	+	
30	Eighteen months	Seventeen months	−	−	
32	Two and one half years	Seventeen months	−	+	
11	Not known	One year, injections	−	−+	No treatment for nine years
50	Ten years	Eight months, mixed	−	+	
52	Eighteen months	One year	−	+−	No treatment for eighteen months
80	One year	Eleven months	−	+	No treatment for eighteen months
130	Three years	Eleven months	+	+−	No treatment for twenty-three years
147	Twenty five years	Two years	+	+	
213	Eight years	Two years, mixed	+−	+−	Treatment stopped
314	Two years	Two years	+	+	Same as 34A, treatment stopped two months ago
316	Two years, two months	Two years, two months	−	+	
219	Sixteen years	Seven months, mixed, lately, some before	−	+	Treatment stopped
164	Three years	One year, continuous, some before	−	−	

No.	Duration of disease	Treatment			Remarks
16B	Three years, two months	One year, continuous, some before	++	++	Same as 16A, treatment stopped two months ago
280	Twenty-two years	"Fair"			
203	Seventeen months	One year	++	+++	Hemiplegia one year ago
0	Three years	Three years	+-	+-	No treatment for past year
24	Four years	Three years	+-	+-	
53	Eight years	Five years	-+	-+	
111	Twelve years	Four years	-+	+-	No treatment for seven years
127	Eleven years	Three years, total	+-	+-	Had gumma of testicle one year ago
129	Twenty years	Three years, total	++	-+	
157	Thirteen years	Well	--	--	Relapse one year ago, continuous treatment since
233	Twelve years	Two years, nine months, total	--	--	
251	"Several years"	"Well"	--	+-	
206	Nine years	Eleven courses, extending over two years			
271	Twelve years	Three years, continuous, four years, intermittent	++	+	
274	Twelve years	Three years	+-	++	
333	Three years, three months	Three years, injections and inunctions	++	++	Negative reaction three months ago, test made by Dr Noguchi. No treatment for past two months
334	Two years, five months	Two years, five months	-+	-+	Had many relapses, last one nine months ago
359	Seventeen years	Four and one-half years, intermittent			
395	Denied	Two and one-half years, injection, Hg salicylate	-	-	Had symptoms of spinal cord syphilis which have disappeared under treatment
419	Twenty years	Well	++	++	Now has melancholia
425	Eleven years	Four years	--	--	
449	Nine years	Five years, continuous	+-	+-	No treatment for six years
459	One year, nine months	One year, eight months	++	++	
461	Twelve years	Seven courses, irregular	++	++	Had several relapses
463	Twelve years	Nearly continuous for twelve years	+-	+-	Very resistant to treatment
465	Two years	Two years, protoiodid pills	++	++	
475	Six years	Six years, pills	++	++	
480	Twenty years	Irregular	--	--	
490	Thirty years	Fairly well	--	--	
515	Three and one half years	Sixty injections, two years, mixed	+-	+-	
530	Six years	Three years, pills, eight months, injections, twenty inunctions	++	++	
536	Two years	Sixty inunctions, one year protoiodid pills	++	++	

TABLE 5 — WASSERMANN AND NOGUCHI REACTIONS IN VISCERAL SYPHILIS

Number	History of Infection	Diagnosis	Symptoms	Treatment	Wassermann	Noguchi	Remarks
10	2 years ago	Tenosynovitis	Swelling and tenderness	14 months	−	+	
10	7 years ago	Hemiplegia	Paralysis	Not known	+	+	
65	5 years ago	Periostitis	Pain and irregularity over tibia	Poorly	+	+	
73	Denied	Hepatitis	Jaundice, enlarged liver	None	+	+	Improved on KI X ray showed gumma like shadow.
81	Denied	Gumma of tibia	Tumor over tibia,	None	+	+	
117	Denied	Cerebrospinal syphilis	Not stated	Fair	±	+	Is improving under treatment
118	20 years ago	Aortic valvular disease	Aortic regurgitation	6 injections Hg salicylate	+	−	
110	Denied	Cerebrospinal syphilis	Not stated	6 mos injections Hg salicylate	±	+	Clinical diagnosis favored syphilis
137	25 years ago	Syphilis of spleen	Tumor of spleen, enlarged glands	1 year at beginning	+	+	
140	Chancroids(?) 9 years ago	Arterial sclerosis	Not stated	Little	+	+	
143	Denied	Meningeal syphilis	Headaches at night, irregular pupils	None	−	+	Husband had syphilis 9 years ago, now has general paralysis
176	Probably by husband	Not stated	"Many surgical operations"	None	−	−	
181	Indefinite	Syphilitic hepatitis	Enlarged liver	Fair	++	+	
182	23 years ago	Aortic valvular disease	Aortic regurgitation	Not stated	−	−	Rapidly improved under antisyphilitic treatment
187	Denied	Hemiplegia	Paralysis, aphasia	Not stated	+	+	
183	"Warts" 10 years ago	Syphilitic spinal paralysis	Paralysis	50 injections Hg salicylate	±	−	5 years ago, facial paralysis, 3 years ago stiff pupils
193	20 years ago	Aneurism of aorta	Not stated	Not stated	+	+	Bauer +
195	Denied	Aortic valvular disease	Aortic roughening	Not stated	±	+	
202	Denied	Syphilitic orchitis	Enlarged testicle	Not stated	−	−	Bauer — Histologic examination of testicle showed spirochete Patient 60 years old
211	20 years ago	Hemiplegia	Paralysis	1 month	−	−	

No.	History	Diagnosis	Symptom	Duration			Notes
217	Indefinite	Aneurism of aorta	Not stated	Not stated	-	-	Bauer -
216	Indefinite	Aortic valvular disease	Aortic regurgitation	Not stated	-	-	Spinal fluid showed weak reaction
178	Denied	Disseminated sclerosis	Not stated	None	+-	+-	
226	Denied	Optic atrophy	Blindness	Not stated	+-	+	Bauer +— Noguchi globulin test +
227	Denied	Gumma of clavicle	Tumor over clavicle	None	++	++	
229	Indefinite	Cerebral syphilis	Not stated	Not stated	-	-	
217	Sore 20 years ago	Aortic valvular disease	Aortic regurgitation	6 months	-	+	No history of secondaries
280	4 years ago	Arthritis	Pain and swelling of knee	6 months	-	-	
281	Denied	Hemiplegia	Paralysis	None	++	+-	Patient 26 years old Improved under KI
234	Indefinite	Sclerosis of cord	Ataxia, increased reflexes	None	++	++	
291	Denied	Cerebral syphilis	Headaches, worse at night	None	+-	-	
300	"One miscarriage"	Cerebral syphilis	Headaches, worse at night	None	-	+	
310	1 year ago	Hemiplegia	Paralysis	1 week	++	++	
311	14 years ago	Myelitis	Not stated	4 months	+	+	
319	Denied	Syphilitic periostitis	Pain and irregularity over tibia	None	++	++	
341	1 year ago	Chronic arthritis	Pain and swelling of knee	Little	++	++	
351	13 years ago	Hemiplegia	Paralysis	Not known	++	++	
352	"Several miscarriages"	Syphilitic osteomyelitis	Chronic sinuses	None	++	+	Infection probably placental Had chronic sinuses in several places not benefited by surgical treatment
371	8 years ago	Pachymeningitis or tabes	Spastic gait, partial paralysis	3 mos., irregular	-	++	Bauer - Amount of serum used contained 5 units of hemolysin for sheep cells, enough to mask 1 unit of syphilitic antibody
375	Probably by husband	Ocular palsy	Blindness	Much in past 2 years	-	-	
357	Sterility	Aortic valvular disease	Aortic regurgitation	Not stated	-	-	
389	Probably congenital	Syphilitic encephalitis	Progressive spastic diplegia	None	+-	+	
390	Denied	Syphilitic encephalitis	Headaches, Jacksonian epilepsy	Not stated	+	++	Child 3 years old
393	Denied	Syphilitic orchitis	Enlarged testicle	None	++	-	

TABLE 5—WASSERMANN AND NOGUCHI REACTIONS IN VISCERAL SYPHILIS —Continued

Number	History of Infection	Diagnosis	Symptoms	Treatment	Wassermann	Noguchi	Remarks
103	Indefinite	Cerebrospinal syphilis	Not stated	Not stated	–	+	
109	Denied	Syphilitic iritis	Failing vision	Little	++	++	
417	4 years ago	Gumma of testicle	Enlarged testicle	2 years, irregular	++	++	
414	Denied	Syphilitic periostitis	Pain and swelling over tibia	None	++	++	
427	25 years ago	Hemiplegia	Paralysis, aphasia	Not stated	+	+	
410	Chancroid(?) 20 years ago	Hemiplegia	Paralysis, systolic murmur at apex	Not stated	+	–	
411	Denied	Paraplegia	Weakness, weakness of bladder	Considerable mixed	++	–	
442	Denied	Paraplegia	Paralysis, weakness of bladder	Little	++	++	
453	Denied	Not stated	Ataxia	Considerable	–	–	Acute ataxia 10 years ago cleared up under antisyphilitic treatment
470	11 years ago	General arthritis	Arthritis	None	++	++	
500	Denied	Syphilitic periostitis	Pain and swelling over tibia	None	–	–	Bauer + Serum hemolytic to human erythrocytes
503	Denied	Syphilitic hepatitis	Enlarged liver, jaundice	None	–	–	Bauer +
504	"Many years ago"	Aortic valvular disease	Headaches, aortic roughening	Not stated	+	+	
508	Denied	Syphilis of cord	Atrophy of tongue, pain in legs	None	+	+	Bauer +
510	Denied	Hemiplegia	Gradual paralysis, ankle clonus, no Babinski	None	+	+	Bauer +
518	25 years ago	Syphilitic meningitis	Feeling of pressure	Full treatment	+	+	Bauer, not enough native hemolysin

TABLE 6—WASSERMANN AND NOGUCHI REACTION IN TABES AND GENERAL PARALYSIS

TABES

No	History of Infection	Treatment	Wassermann	Noguchi	Remarks
28	Seven years ago	Well	+	+	Disease apparently stationary
38	Ten years ago	Continuous for past seven months	–	–	
125	Thirty-one years ago	One month	+	+	
126A	Twenty years ago	Poorly until lately	–	+	Same as 126A, treatment stopped to see if reaction would appear
126B	Twenty years ago	None for past five weeks	+	+	
111	Twenty years ago	Not stated	–	+	No treatment until tabes appeared four years ago
156	Thirteen years ago	Continuous for past four years	–	–	Well marked Charcot joint
183	Sore thirty years ago, no secondaries	Not stated	+	+	
186	Seven years ago	Fifteen injections Hg salicylate, lately	–	+	Bauer — Had gumma of leg six months ago
189	Denied	None	+	+	
210	Denied	Thirty-six injections, Hg salicylate	–	–	Tabetic symptoms not well marked
212	Denied	None	+	+	
232	Denied	None	+	+	
250	Fifteen years ago	Two months	+	+	
292	Denied	Not stated	+	+	
296	Twelve years ago	None	+	+	
302	Twenty-nine years ago	None	+	+	
303	Eight years ago	None	–	–	
304	Denied	None	+	+	
305	Twelve years ago	Ten months	+	+	
306	Fourteen years ago	Not known, considerable	+	+	
307	Eighteen years ago	None	+	+	
308	Twenty-five years ago	None	–	–	
309	Thirty five years ago	None	+	+	
312	Eighteen years ago	None	+	+	
313	Several years ago	Not stated	+	+	
343	Urethritis, followed by secondaries	None	+	+	
350	Denied	None	+	+	
366	Nineteen years ago	Two years	–	–	Also has aortic valvular disease
369	Denied	None	+	+	
410	Twelve years ago	None	–	–	
413	Twenty years ago	Four months injections, Hg salicylate	+	+	
420	Eighteen years ago	Not stated	+	+	
439	Twenty three years ago	Thirty injections Hg salicylate, lately	–	–	
509	Twenty one years ago	Many injections in past year	+	+	Also has aortic valvular disease
517	Denied	None	–	–	Now has colon bacillus sapremia
532	Denied	Not stated	+	+	
535	Twenty-two years ago	Not stated	+	+	

GENERAL PARALYSIS

No	History of Infection	Treatment	Wassermann	Noguchi	Remarks
120	Denied	None	+	+	Marked lymphocytosis in spinal fluid
124	Denied	None	–	+	Early in the disease
171	Denied	None	+	+	Symptoms well marked

TABLE 7.—WASSERMANN AND NOGUCHI REACTIONS IN CONGENITAL SYPHILIS

No	Age	Symptoms	Treatment	Wassermann	Noguchi	Remarks
154	Three years	Idiocy, anemia, enlarged liver, frontal bosses	Little	+	++	Can not tolerate mercury
225	Eight years	Deafness, Hutchinson's teeth, jaundice, chorea	Little	++	+	
234	Ten years	Saddle nose, Hutchinson's teeth, frontal bosses	None	++	++	Eight brothers and sisters died in infancy. Father has optic atrophy
237	Ten years	Congenital keratitis	None	++	+	

TABLE 8.—WASSERMANN AND NOGUCHI REACTIONS IN SPINAL FLUID FROM SYPHILITIC PATIENTS

No	Diagnosis	History of Syphilis	Evidence of syphilis	Wassermann	Noguchi	Remarks
91	Tuberculous meningitis	Several years ago	Old specific scars	+	+	
98	General paralysis	Seven years ago	Not stated	—	—	
117	Cerebrospinal syphilis	Denied	Not stated	—	—	Blood positive one month earlier
165	Uremia, syphilis secondary	Not obtained	Rash	—	—	Patient died of uremia next day
178	Disseminated sclerosis	Denied	Not stated	+—	—	Blood showed weak positive reaction
315	Congenital syphilis?	Not reported	"Rash that looks specific"	—	—	From child five months old
316	Congenital syphilis?	Not reported	"Rash that looks specific"	—	—	From child six months old
84	Congenital syphilis	Not reported	Anemia, malnutrition, enlarged liver, rash	+	—	From child three months old

TABLE 9.—WASSERMANN AND NOGUCHI REACTIONS IN BLOOD AND SPINAL FLUID FROM AUTOPSIES

No	Anatomical Diagnosis	BLOOD SERUM Evidence of Syphilis	Wassermann	Noguchi	Remarks
63	Mitral valvular disease	No other	+—	+—	
219	Aortic valvular disease, syphilitic hepatitis	Aortic disease, cirrhosis of liver	++	+	
344	"Syphilis"	Rupial lesions	±	—	
374	Tuberculosis, chronic pulmonary aortitis, pericarditis, chronic nephritis	Aortitis, cutaneous syphilid	+	—	
		SPINAL FLUID—SYPHILITIC			
139	Syphilis, visceral	Syphilitic pneumonia, chronic myocarditis, syphilitic cirrhosis of liver, interstitial orchitis	—	++	
185	Syphilitic meningitis	Marked thickening of pia	+	+	Fluid removed five days postmortem
201	Aortic valvular disease	Thickening of aortic valves	—	—	
294	Pneumonia, syphilitic aortitis	Aortitis	—	—	
364	Tuberculosis, chronic pulmonary, syphilitic hepatitis	Hepatitis, cutaneous syphilid	—	++	
		SPINAL FLUID—NOT SYPHILITIC			
251	Pneumonia, granular ependymitis	None	—	—	
252	Carcinoma of pylorus	None	—	—	
253	Hemorrhage, cerebral, arterial sclerosis	None	—	—	
295	Tuberculosis, chronic pulmonary, softening of pons	None	—	—	
317	Internal hydrocephalus	None	—	—	

Primary, secondary, tertiary, latent, visceral and congenital syphilis are tabulated, as also tabes and general paralysis To these are added the results of the examination of spinal fluids of syphilitics obtained by lumbar puncture during life and of spinal fluids and blood obtained at autopsy The tabulation is arranged to show clearly any difference in results by the two methods When a difference was found at first examination the reaction was repeated to control the methods and only the final result is published

Summarized the results are given in Table 10

TABLE 10 —SUMMARY OF COMPARISON OF WASSERMANN AND NOGUCHI METHODS

Stage	Total Number	Wassermann				Noguchi			
		Positive		Negative		Positive		Negative	
		No	%	No	%	No	%	No	%
Primary	16	13	81	3	19	13	81	3	19
Secondary	76	70	92	6	8	74	97	2	3
Tertiary	45	37	80	8	20	40	88	5	12
Latent, (none or little) treatment	39	25	64	14	36	25	64	14	36
Latent, fairly well treated	46	21	46	25	54	27	60	19	40
Visceral	60	41	68	19	32	40	66	20	34
Tabes	38	22	55	16	45	26	68	12	32
General Paralysis	3	2	67	1	33	3	100	0	0
Congenital	4	4	100	0	0	4	100	0	0
Autopsy, blood	4	4	100	0	0	2	50	2	50
Autopsy spinal fluid	5	1	20	4	80	3	60	2	40
Spinal fluid from syphilitic patients	8	3	37	5	63	1	12	7	88

These results show that the Noguchi modification in 5 to 20 per cent of the cases was more delicate

With the spinal fluids the Wassermann method seems to give a better result as is also the case with the blood obtained at autopsy The number of postmortem bloods, however, is so small that definite conclusions can not be made, but that this material is satisfactory for the Wassermann reaction has been demonstrated by Pick and Proskauer,[26] and Fraenkel and Much [27] The latter, however, found that the blood of scarlet fever obtained from the cadaver gave in five out of twelve samples a positive reaction

CONTROLS

In the course of this work a very large number of control bloods have been examined with negative results by both methods These may be classified according to the nature of the illness under the headings "Dermatologic," "Medical," Surgical" and "Neurologic" The four groups include ninety-one bloods and sixteen spinal fluids, as follows

Blood Controls, Dermatologic—Acne vulgaris, 4, pityriasis versicolor, 1, dermatitis herpetiformis, 2, pyogenic dermatitis, 1, eczema, 3, erythema multiforme, 2, fibroma molluscum, 1. ecthyma, 1, furuncu-

26 Pick L and Proskauer, A   Med Klinik, 1908 iv, 539
27 Fraenkel, E , and Much H   Munchen med Wchnschr , 1908, iv, 2479

losis, 1, herpes zoster, 1, impetigo contagiosa, 1, lupus vulgaris, 1, lupus erythematosus, 1, lichen planus, 1, rosacea, 2, pemphigus, 1, syphilophobia, 1, tuberculosis verrucosa cutis, 1, chronic ulcer of mouth, 1

Blood Controls, Medical—Arthritis deformans, 2, adiposis dolorosa, 1, bronchitis, 1, hepatic cirrhosis, 2, diabetes mellitus, 1; diphtheria, 1; fever (unexplained), 1, cerebrospinal meningitis, 1, tumor of lung, 1, tuberculosis, 7, varicella, 1, meningitis (variety not stated), 1, chronic cardiac disease, 1

Blood Controls, Surgical—Suppurative adenitis, 1, balanitis, 1, chancroids, 9; carcinoma, 11, condyloma acuminatum, 1, gonorrhea, 3, traumatic orchitis, 1, tumor of chest, 1, chronic ulcer of leg, 4

Blood Controls, Neurologic—Cerebral tumor, 3, hemiplegia, 4, headaches, 3, spastic paraplegia, 1, paraplegia, 1, vertigo, 1

Spinal Fluid Controls—Tuberculous meningitis, 9; cerebrospinal meningitis, 1, meningitis (variety not stated), 3, gastroenteritis with meningeal symptoms, 2, alcoholic cerebral edema, 1

The controls which gave a reaction may be divided into three classes (A) scarlet fever, (B) leprosy and (C) miscellaneous

A The frequent occurrence of a positive reaction in scarlet fever has been much discussed and, as the etiology of scarlet fever is unknown, has aroused some conjecture as to whether or not a spirochete may be concerned in the causation of this disease Much and Eichelberg[28] report as positive, 50 per cent of the scarlet fever bloods which they examined Halbertstaedter, Muller and Reiche[29] report five out of ten cases, and Butler,[30] four cases, positive On the other hand, many others report they have never obtained the reaction in this disease My results are given in Table 11, where it may be seen that in eight cases of scarlet fever the Wassermann method gave positive results in 12 per cent and the Noguchi in 37 per cent

B Leprosy has been studied with the Wassermann technic by various observers The most extensive observations are by Jundell, Elmkvist and Sandman,[31] who studied twenty-six cases, of which four gave the reaction Of the four positive cases, three were of the tubercular and one of the maculo-anesthetic type My results are shown in Table 12

28 Much, H, and Eichelberg, F Med Klinik, 1908, iv, 671
29 Halbertstaedter, L, Müller, E, and Reiche, A. Berl klin Wchnschr, 1908, xlv, 1917
30 Butler, W J New York Med Jour, 1909, lxxxix, 207
31 Jundell I, Almkvist, A, and Sandman, F Centralbl f inn Med, 1908, xxx, 1181

TABLE 11.—WASSERMANN AND NOGUCHI REACTIONS IN SCARLET FEVER

Number	Day of Disease	Wassermann	Noguchi
107	7th		—|+
198	7th	—|+	—|+
199	5th		++
200	5th		+
262	6th		—
263	8th		—
278	6th		—
279	3d		—|+

TABLE 12.—WASSERMANN AND NOGUCHI REACTIONS IN LEPROSY

No	Form of Disease	Wassermann	Noguchi	Remarks
258	Mixed	+	++	Marked general adenopathy
327	Tubercular	—	—|+	Repeated with same result
405	Maculo anesthetic	—	++	Repeated with same result, but negative with inactivated serum

TABLE 13.—OTHER CASES NOT SYPHILITIC GIVING A POSITIVE REACTION

No	Diagnosis	Wassermann	Noguchi	Remarks
21	Arthritis deformans	—	+	Also done by Dr Noguchi with same result
22	Arthritis deformans	—|+	+	Also done by Dr Noguchi with same result
93	Varicella, congenital syphilis?	+	+	Probably has congenital syphilis Evidence Malnutrition, notched teeth, frontal bosses
169	Tuberculosis verrucosa cutis	—	—|	Diagnosis confirmed by histologic examination
208	Chancroids, eczema	—	+|	Had chancroids one year ago, no secondary symptoms
231	Dilatation, chronic cardiac	—	+|	One clinical diagnosis was acute aortitis All venereal disease and symptoms denied
273	Leucoderma	—	++	Boy, no further evidence of syphilis
338	Normal man	—	+	Father of boy with brain tumor, denies all symptoms of venereal disease
340	Amyotrophic lateral sclerosis	—	+|	Foreigner, in whom history was difficult to obtain
381	Carcinoma of penis, before operation	—	+	Microscopic examination confirmed diagnosis
381	Same case after operation	—	+	Negative with inactivated serum
182	Generalized dermatitis	—	+	Negative with inactivated serum
483	Erythromelalgia, arterial sclerosis	—	+	Negative with inactivated serum, denies all evidence of syphilis
384	Epileptiform attacks	—	+|	Negative with inactivated serum
506	Nephritis, chronic uremia	—	++	Negative with inactivated serum
516	Monoplegia	—	+	Negative with inactivated serum, no history of syphilis, had gonorrhea several years ago
519	Traumatic arthritis	—	+	Negative with inactivated serum, patient has general adenopathy, no other specific symptoms
521	Herpes progenitalis	—	+	Negative with inactivated serum, had herpes four weeks ago, no other specific symptoms

Of three cases, one gave the Wassermann, two the Noguchi reaction With the Wassermann method inhibition was only partial, while with the Noguchi it was complete

C We now come to a class of cases, the miscellaneous group, which are of the utmost importance in the determination of the reliability of this test These are summarized in Table 13

Among these, only one gave the Wassermann reaction This patient was a boy with varicella who presented strong evidence of congenital syphilis No family history pointing to syphilis could be obtained and, unfortunately, the case disappeared from observation so that the test could not be repeated after the varicella had subsided Hence it could not be accurately determined whether this disease was the cause of the reaction or not Two cases of arthritis deformans gave a positive Noguchi reaction, this is of interest in that Noguchi has found that his test frequently gives inhibition in this disease In most of the other cases giving the reaction the blood was sent for diagnosis, the clinician suspecting syphilis in each case, but having little evidence to substantiate this diagnosis Syphilis could not be absolutely excluded in any instance

Noguchi ascribes great importance to the various grades of reaction Complete or marked inhibition he regards as diagnostic, while slight inhibition he considers as an indication for further treatment in those cases in which the diagnosis of syphilis has previously been made The seventeen cases (No 381 is considered as one) reported in Table 13 show three with complete and eleven with marked inhibition, or a total of fourteen diagnostic reactions This number of positive results in non-syphilitics would appear to be too high for unconditional acceptance of the method

The cause of the increased sensitiveness of the Noguchi method is apparently due to two factors First, a small antibody content is not masked by the presence of a large amount of native hemolysin, second the serum used is not inactivated Sachs[32] last year called attention to the fact that active serum gave a stronger reaction than inactive, but that with such serum positive reactions were obtained in non-syphilitic individuals Boas[21] reported similar results and has shown that active serum is two to four times more powerful than inactive, and that the reaction appears earlier and persists longer with active serum He further presented a list of forty-five non-syphilitics giving a positive reaction with active serum, but reacting negatively when the same serum was inactivated From his work he concludes that it is not safe to employ active serum and condemns the Tschernogubow method because such serum is

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32 Sachs Verhandl d deutsch Dermat Gesellsch X Kong, 1908 p 167

used Application of such observations and deductions to the study of the Noguchi method leads to the conclusion that both the increased number of specific reactions and the few non-specific ones are due to the use of active serum This does not destroy the value of the Noguchi method, because inactive serum can readily be employed instead of active Referring to Table 13 it will be noted that the last eight cases gave results corresponding to the Wassermann reaction when inactive serum was used In these tests the active serum was employed in the amount of one drop, which corresponds to 0 02 c c With the inactive serum 0 08 c c was used, the proportion of human serum to guinea-pig serum being two to one, the same as is employed in the Wassermann reaction I believe the use of active serum explains the non-specific reaction with the Noguchi method in some cases and am now working on this phase of the question The results of such work will shortly be published

When one compares the different methods, the advantages of Noguchi's technic make it most attractive The small amount of serum required, the ease of preserving the reagents, and the fact that one does not require a constant supply of sheep's blood, are important points in its favor, but to put it into the hands of untrained workers seems to me most undesirable Good controls are needed for each test, and the more that are introduced the more accurate are the results Only those having special training in hemolytic work and serum diagnosis can appreciate the difficulties of such a complicated method To obtain reliable results the work should be done under favorable conditions by one who has been trained in laboratory methods To place the material in the hands of inexperienced workers would bring the method into disrepute, for results would be too uncertain The enormous responsibility assumed by one in making a diagnosis would seem to require at least as much experience as is expected of a bacteriologist or clinical laboratory worker

CONCLUSIONS

1 The Wassermann reaction is a fairly definite diagnostic measure A positive reaction practically always means syphilis Negative findings give only presumptive evidence of the absence of syphilis

2 The Bauer modification is not reliable because of the inconstant content of native hemolysin to sheep cells A large anti-sheep hemolytic content will mask a partial complement fixation

3 The Noguchi reaction is more readily applied and the materials are more easily procured and kept than with the Wassermann method It is also more sensitive than the Wassermann reaction This increased sensitiveness, however, sometimes causes a positive reaction with non-

specific sera which give a negative Wassermann reaction   Experiments now under way seem to indicate that this may be avoided by the use of inactive serum

THE MUCH-HOLZMANN SERUM REACTION IN INSANITY *

A J ROSANOFF, M D

KINGS PARK, N Y

While the present trend in psychiatry seems to be mainly in the direction of psychogenic causes in the etiology of the so-called functional insanities, yet from time to time cases are reported or in other ways facts are brought to light which would indicate that the toxic theory of the origin of these conditions is, at least for the present, not to be definitely discarded

In a brief preliminary communication published a short time ago[1] H Much describes a new serum reaction which he found to be almost specific for dementia præcox and manic-depressive insanity This reaction is based on the alleged power possessed by the serum in cases of these conditions of inhibiting the hemolytic action of cobra venom on human red blood corpuscles

With the collaboration of W Holzmann he examined the blood in four hundred cases, including, on the one hand, various forms of insanity and, on the other hand, many different physical diseases without mental disturbances, and found this reaction always present in cases of manic-depressive insanity and dementia præcox, regarded as such in the strictly limited classical sense, according to Kraepelin, he also found it in some cases of epilepsy with periodically recurrent mental disturbances, further, he found it in sane persons belonging to families in which insanity existed

These remarkable results led me to apply this reaction in a series of cases of various forms of insanity at the Kings Park State Hospital, and for the purposes of control and comparison, in a number of normal persons

The technic of the reaction, as described by Much and Holzmann, is as follows 0 35 c c of serum is mixed with 0 25 c c of a 1.5000 solution of cobra venom, to this is added 0 5 c c of a 10 per cent suspension of human blood corpuscles (prepared by allowing blood to flow into normal salt solution containing 2 per cent of sodium citrate, washing the cor-

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puscles twice with normal salt solution and finally making a suspension of the desired strength), this mixture is placed in the incubator for two hours and then in the refrigerator for twenty-two hours, at the end of which time the reading is taken

I have found it convenient to modify the technic to a slight extent The stock solution of cobra venom was prepared in the manner suggested by Much and Holzmann namely by making a 2 per cent solution of the dried venom in distilled water and then adding an equal volume of glycerin, this solution was preserved by the addition of a few drops of chloroform and was further protected against putrefaction by being kept in the refrigerator For use it was diluted with normal salt solution until a solution of the strength of 1 5000 was obtained The cobra venom which I used was from a specimen in possession of Dr H Noguchi of the Rockefeller Institute, by titration this specimen of venom was found to be so actively hemolytic that the relative quantity of the solution employed in the reaction had to be reduced to a little over one-half of that employed by Much and Holzmann The proportions of the other ingredients in the reaction—serum and suspension of blood corpuscles—were not changed, but their absolute quantities were reduced in order to avoid taking unnecessarily large quantities of blood

From 1 to 1 5 c c of blood taken from the lobe of the ear supplied the amount of serum which I used in the reaction, namely, 0 2 c c , to this was added 0 08 c c of the 1 5000 solution of cobra venom and 0 3 c c of blood corpuscle suspension In the control tubes 0 2 c c of normal salt solution was used in place of serum

Complete hemolysis occurred in the control tube almost always before it occurred in any of the other tubes, so that it became evident that practically all serums had some slight power of inhibiting the hemolytic action of cobra venom on human blood corpuscles On the other hand, complete inhibition of hemolysis did not occur in a single instance Thus the reaction became merely a test of the relative degree of this inhibiting power possessed by a given serum Therefore, I took the readings, as suggested by Much and Holzmann, at the end of twenty-four hours (two hours in the incubator and twenty-two hours in the refrigerator), on thoroughly shaking the tubes In taking the readings in this way I found no difficulty in distinguishing between a strongly positive reaction and a distinctly negative one, but in many instances of moderate inhibition of hemolysis I was unable to make the distinction satisfactorily, for this reason, in tabulating my findings, I counted as positive (+) all cases in which the mixture in the tubes on shaking showed complete

opacity, as slightly positive or doubtful ($\underline{+}$) all cases in which there was opacity with a distinct laked appearance, and as negative (—) all cases in which the tubes showed any degree of transparency

The cases used in this investigation were carefully selected from the large amount of such material that is available at this hospital with a view to excluding all but perfectly typical cases in which the diagnoses were as nearly certain as possible, thus in all the cases of general paresis the clinical diagnosis had been corroborated by lumbar punctuie To this there were, however, five exceptions in four cases there were symptom-complexes resembling manic-depiessive insanity, but running a chronic course with no remissions oi alternating phases, these cases form in the table of findings a separate group designated "chronic psychoses allied to manic-depressive insanity", and one case, which presented a clinical picture of dementia præcox, showed, in addition, some evidences of organic brain disease and appears in the table as "psychosis allied to dementia præcox "

The specimens of serums assumed to be normal were obtained from officers and employees at this hospital, who kindly consented to give some of their blood not only for the purpose of furnishing the serum, but also for preparing the suspension of blood corpuscles used in the reaction I take this opportunity of acknowledging my indebtedness to them

As will be seen from the figures in the table, the serums of some of the apparently normal persons showed a positive reaction The statement of Much, to the effect that this reaction may be found in the serums of sane persons belonging to families tainted with insanity, has already been referred to I regret to have found it impracticable to inquire into the matter of insane heredity in my cases The following table shows my findings

TABLE 1 —MUCH-HOLZMANN REACTION

Mental Disorders	Total No	+	$\dfrac{+}{2}$	—
Dementia præcox	38	22	2	14
General paresis	35	5	3	27
Epilepsy with insanity	12	2	4	6
Polyneuritie psychosis	8	1	1	6
Manic depressive insanity	15	0	1	14
Involution melancholia	10	1	0	9
Senile dementia	11	0	1	10
Arteriosclerotie brain disease	6	0	3	3
Infantile cerebral palsy	5	1	2	2
Paranoic condition	2	0	0	2
Cerebral syphilis	1	0	0	1
Chronic psychoses allied to manic depressive insanity	4	2	1	1
Psychosis allied to dem prec	1	0	0	1
No psychosis	37	3	5	29

In 109 of the above cases the serum was examined also for the Wassermann reaction   In order to determine whether there is any relationship between the Much-Holzmann reaction and the Wassermann reaction I have tabulated my results

TABLE 2 —MUCH-HOLZMANN AND WASSERMANN REACTION

Wassermann Reaction	No of Cases	Much-Holzmann Reaction					
		+		+ −		−	
		No	%	No	%	No	%
+	26	8	30 8	2	7 7	16	61 5
+ −	13	1	7 7	2	15 4	10	76 9
−	70	12	17 1	10	14 3	48	68 6

SUMMARY OF FINDINGS

1   Practically all human serums possess the power, in a more or less pronounced degree, of inhibiting the hemolytic action of cobra venom on human blood corpuscles [2]

2   A comparatively high degree of this power, which constitutes the basis of Much and Holzmann's reaction, is not strictly specific for any psychosis, being found with greater or less frequency in almost all psychoses and in the blood of a considerable percentage of persons who are apparently normal (8 1 per cent. in the series cited in this paper)

3   This reaction was present in more than half of my series of cases (57 9 per cent) of dementia præcox   As it appears to be much more common in this condition than in any other, it may prove to be a diagnostic aid, it would seem that the presence of this reaction in a psychosis should add, in the consideration of the diagnosis, some degree of probability in favor of dementia præcox

4   Of a series of fifteen typical cases of manic-depressive insanity not one gave a positive reaction, and in only one was the reaction doubtful, being clearly negative in all the rest   I might add here that two of the patients had recovered from their psychosis when their blood was examined

5   There is apparently no relationship between the Wassermann reaction and the Much-Holzmann reaction

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2   For a complete presentation of the subject of venom hemolysis see Noguchi Snake Venoms, chap xvi (published by the Carnegie Institution, Washington, D C , 1909)

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THE NATURE OF SHOCK

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NEW YORK

In the clinical literature, shock designates a group of grave symptoms which frequently lead to the death of the individual At the postmortem examination no anatomic changes can be detected which would account for death and the grave symptoms preceding it The fatal disturbance underlying the phenomenon of shock is, then, exclusively of a functional nature From a purely scientific point of view, shock is, therefore, a subject pre-eminently belonging to the domain of pathologic physiology It should be mentioned that the term shock employed in normal physiology is not identical with the syndrome in which we are interested here The shock of the physiologists refers to the depression and suppression of spinal reflexes brought about by a direct injury to the cord We shall not stop here to discuss the possibility of a common ground for both forms of shock We wish, on the contrary, to point out one strikingly distinguishing feature physiologic shock is practically not progressive, on the contrary, as a rule, it is fairly rapidly regressive Clinical shock is, as a rule, progressive, although, as we shall see, it is not invariably fatal

In selecting the discussion of the nature of clinical shock as the subject of my present address, it is chiefly my intention to record some experimental facts which we obtained in the course of various series of investigations and which may have some bearing on the interpretation of clinical shock

As an introduction to this report, however, it will be necessary to dwell briefly on the clinical facts of our syndrome and also to review briefly the theories as to the nature of shock now in vogue and the experimental facts on which they are based As to the clinical picture of shock I could not do better than to quote the description of a concrete case of shock as lucidly given by Fischer[1] nearly forty years ago .

A strong and perfectly healthy young man was struck in the abdomen by the pole of a carriage drawn by runaway horses No recognizable injury was done to any of the internal organs Nevertheless, grave symptoms made their appearance immediately after the accident The injured man was lying perfectly quiet and paid no attention to anything going on around him His face was drawn and

* Address delivered at the Academy of Medicine of Toronto, April 7, 1908
1 Fischer, H Samml klin Vortr , 1870, No 10, p 119

peculiarly elongated, the forehead wrinkled and the nostrils dilated His weary, lustreless eyes were deeply sunk in their sockets, half covered by the drooping eyelids and surrounded by broad rings The pupils were dilated and reacted sluggishly to light The eyes had a glassy and vacant expression The skin and the visible mucous membranes had a marblelike pallor Large drops of sweat hung on forehead and eyebrows The rectal temperature was subnormal The sensibility of the entire body was greatly reduced, the patient reacted slightly and only to very painful impressions No spontaneous movements of any sort were made by the patient On repeated and urgent requests he showed that he could execute limited, brief movements with his extremities When the limbs were lifted passively and then let go, they fell down like dead The sphincters were intact The urine obtained by catheter was scanty and concentrated, but otherwise normal The almost imperceptible pulse was rapid, irregular and unequal The arteries were narrow and of very low tension The patient answered slowly, reluctantly, and only after repeated urgent questioning His voice was hoarse and weak, but well articulated On being repeatedly questioned, the patient complained of cold, faintness and deadness of all parts of the body When he shut his eyes he felt nauseated and dizzy The respirations appeared irregular, long, abnormally deep, sighing inspirations interchanged with rapid and superficial ones, which were scarcely visible or audible

Recapitulating briefly, the essential symptoms of this typical case of traumatic shock consisted of general profound apathy, reduced sensibility, extreme motor weakness, great pallor, very rapid, small pulse, thready and soft arteries, irregular gasping respirations and subnormal temperature

Fischer does not state the subsequent fate of that patient

Shock brought on by a blow on the abdomen has often had a rapidly fatal termination This is graphically illustrated by the following instances given by Sir Astley Cooper [2]

A man walking through Fleet street (London) one day, happened to quarrel with a woman, when another man came up and gave him a blow in the region of the stomach, which caused almost instantaneous death On dissection, no cause could be found to account for his sudden death

A man belonging to the India House was attempting to lift a weight, when another came up and jocosely said, "Here, stand on one side and let an able man attempt it," and at the same time gave him a slight blow on the stomach, when the poor fellow dropped down and expired His body, on being opened, showed no marks of violence

Similar rapid fatal terminations from shock are reported from injuries to the testicles John Hunter [3] is stated to "have seen a man die almost immediately on the loss of a testicle" Fischer [4] tells that he has seen a strong man dying of shock a few hours after he was bitten in the testicle by a wild horse However, there are some cases with all the symptoms of profound shock which, nevertheless, recover completely

2 Cooper, Sir Astley Lectures on Surgery, 1830, p 9
3 Hunter, John, quoted by Morris Shock, London, 1867 p 13
4 Fischer, H · Samml klin Vortr, 1890, No 10, p 119

Travers,[5] who probably was the first surgical author to use the term shock with the precise meaning attached to it now, writes

Again and again I have left the bedside of patients brought into the hospital pulseless and apparently moribund without any external injury, having suffered falls or blows so serious as to have induced the symptoms of prostration to an alarming extent, and have found them on the succeeding day, to my great surprise, restored to the tone and tranquility of normal health

The shock described in the foregoing instances is generally designated as traumatic shock It is characterized by sudden onset and rapid development of the symptoms following immediately on an injury more or less violently and rapidly executed In recent literature we frequently meet with the term "surgical shock," which has reference to the condition of shock which develops in the course of a surgical operation or soon after it It occurs most frequently in abdominal and brain operations It differs from traumatic shock only in its slower development, although most of the recent writers have dwelt in their description specially on the behavior of the heart and the blood pressure Possibly the pathologic state preceding the operation, the anesthesia and the loss of blood combine to obscure the sharp outlines of shock as seen in purely traumatic cases

As to the theories, the earlier writers spoke in a vague way of the central nervous system as being the seat of the affection Cases of shock produced by mental terror without any physical injury gave support to such a view It was assumed that a strong emotion, as well as a physical commotion, caused some sort of profound molecular changes in the brain

The first well-defined theory was brought forward by Fischer,[6] who founded it on the well-known experiments of Goltz Repeated strokes on the abdomen of a frog causes stand-still of the heart and paralysis of the arteries and the veins of the abdominal cavity, which is brought about by reflex paths Fischer assumed then that traumatic shock consists of a vasomotor paralysis, especially of the splanchnic area, where the bulk of the body's blood is accumulated, with a consequent anemia in other parts Shock was a hemorrhage into the body's own large veins. According to Fischer, the vascular disturbance was the primary cause, all other symptoms were secondary phenomena due to the consequent anemia of the peripheral parts

Another theory was that of Groeningen,[7] who assumed that all the nerve centers were equally affected, not by paralysis but by exhaustion

5 Travers Inquiry Concerning Constitutional Irritation London, 1827
6 Fischer H Samml klin Vortr , 1890, No 10, p 119
7 Groeningen, quoted by Warren Surgical Pathology

brought on by the traumatic over-stimulation Mansell Moulin is cred-
ited by Warren[8] with the theory that the various nerve centers of the
body were not exhausted, but inhibited

These and some other theories were simply construed at the writing
desk of their authors It is only within the last decade that more or less
efficient attempts were made to study the nature of shock by the experi-
mental method As far as I can see, the experimentation led up only to
a study of surgical shock, that is, to a shock which developed gradually,
similar to that occurring in surgical practice, and there are no reports
of experiments in which shock developed as rapidly as in the traumatic
cases

The most extensive series of experimental work on the problem of
shock was carried out by George W Crile The protocols of the experi-
ments and the conclusions drawn from them are published in two large
monographs[9] The experiments were made on dogs while under ether
anesthesia The various tissues, like skin, muscle, nerve, bone, etc, in
the various parts of the body head, neck, thorax, abdomen, extremities,
etc, were subjected to various strong mechanical irritations, to burning
and to electric stimulations, with a view to study their effects on
blood pressure and on the production of shock The effects of these
various stimulations on respiration and cardiac activity were also studied
but less extensively The chief facts reported by Crile are as follows

Strong irritations, like cutting, tearing, burning the skin all over the body,
except over the abdomen and testicles, and of the sensory nerve trunks cause,
as a rule, a more or less strong rise of blood pressure during the stimulation
Cutting the skin over the abdomen or over the testicles causes as a rule a fall
of blood pressure Opening the abdomen, exposing and handling the intestines,
cause a continuous fall Repeated stimulation of the skin or nerve trunks leads
at first to a diminution in the increase in the rising effect, then comes a stage in
which the stimulation causes primarily a fall and finally ends up with a stage in
which stimulation has no effect whatsoever on the blood pressure At that stage
usually the blood pressure is very low and can not be permanently improved by
any medicinal or other treatment This is, according to Crile, the stage of
complete surgical shock The development of shock is hastened by the strength
of the repeated stimuli and by the amount of tissue involved in the stimulation,
under all circumstances, however, its development is always a slow and gradual
one

The characteristic signs of surgical shock are, according to Crile, the
very low blood pressure and the impossibility of influencing the pressure
by any stimulation The cause of it is exhaustion, the breakdown of the
vasomotor center by the preceding over-stimulation Adrenalin may

8 Warren, John Collins Surgical Pathology 2d ed, 1900
9 Crile, George W   An Experimental Inquiry into Surgical Shock, Philadel
phia, 1899, also Blood Pressure in Surgery, Philadelphia and London, 1903

temporarily raise the blood pressure by a contraction of the muscles of the wall of the blood vessels, also transfusion or peripheral mechanical pressure may raise the blood pressure simply by hydraulic principles, but the rise will be only temporary The pressure will not be self-sustaining on account of the complete exhaustion of the vasomotor center

According to Crile, then, failure of blood pressure is the primary and sole cause of all the symptoms of shock, and this failure has as its cause solely the exhaustion of the vasomotor center The cardiac and respiratory failures and other phenomena are only secondary consequences or subsidiary factors to the primary cause, the exhaustion of the vasomotor center

Crile makes a distinction between shock and collapse In the latter low blood pressure and all the other symptoms of shock may be present But the onset of collapse, Crile says, is sudden and the conditions are amenable to stimulation because the vasomotor center is not exhausted but only depressed and can be raised to activity by stimulation As far as I can see, the difference between shock and collapse, according to Crile, is as follows

The onset is gradual in shock and sudden in collapse Collapse may have its origin in cardiac, respiratory or vasomotor insufficiencies, shock is of vaso motor origin only Collapse is amenable to stimulants and stimulation, shock is not In shock the vasomotor center is exhausted, in collapse, if this center is affected, it is only functionally depressed

I shall not discuss here whether it may be possible to distinguish at the bedside of a human patient between shock and collapse, although such a distinction might be of practical vital importance, since, according to Crile, stimulants like strychnin or alcohol may hasten the end in shock, but may save life in collapse I wish only to call attention to the fact that shock as described by Crile fits only surgical shock, and that traumatic shock, especially as was described classically by earlier writers, had, on the contrary, mostly, if not always, a sudden onset I hardly think that Crile assumes that all these cases were only of the collapse variety But I could not find in his writings a discussion of this apparent discrepancy

Crile's results and teachings have been widely accepted in the surgical world, especially in the United States and England They were endorsed by such prominent experimental surgeons as Victor Horsley and Harvey Cushing They were given a wide prominence by the lectures of Mummery[10] in England and they have found their way into all new text-books

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10 Mummery P Lockhart Lancet, 1905 i p 696, ff

Within the last few years, however, some divergent views made their appearance Boise,[11] in the United States, and Malcolm,[12] in England, who are willing to accept the facts as they are reported by Crile, attempted to interpret them differently They believe that the low blood pressure and the venous stasis observed in surgical shock need not be due to paralysis of the blood vessels and an exhaustion of the vasomotor center, but, on the contrary, can be and are the outcome of a high stimulation of the center and a strong contraction of the heart and the arteries The theories of these writers are not supported by any observations or experimental tests of any weight, and we shall not enter into a discussion of the validity of their theoretical arguments

I shall mention particularly, however, some important experimental work recently done by very competent physiologic investigators W H Howell[13] undertook to produce shock in anesthetized dogs either by prolonged handling of the intestines or by applying heat to a large surface of the skin or by operations on the brain He was frequently confronted with the experience that what produced shock readily in one animal singularly failed to have any effect on another animal Howell distinguished two forms of shock, cardiac and vascular In some cases the pulse would be feeble and very rapid, while the blood pressure would remain of a fairly good height In other animals the blood pressure would drop to forty or twenty millimeters of mercury, while the pulse would also be greatly accelerated Cardiac shock could occur without vascular depression, while vascular shock was always accompanied by cardiac shock Howell thinks that neither the vascular nor cardiac shock was due to an exhaustion of the medullary centers, for in neither case were there any signs of a preceding over-excitation He assumes that both cases of shock are due to an inhibition of the centers in the medulla, that is an inhibition of the tonus of the vagus center which causes acceleration of the heart and an inhibition of the vasomotor center which leads to vascular shock

Howell, then, like Crile, sees in the disturbance of the circulation the essential characteristic of shock, but differs from him in that he does not assume that the vasomotor center is exhausted and that he lets the cardio-inhibitory center share in the causation of the shock

11 Boise Amer Jour Obstet , 1907, Iv p 1
12 Malcolm Lancet Aug 26 1905, ii also Lancet, 1907, i, p 407
13 Howell W H Contributions to Medical Research, dedicated to Victor C Vaughan, 1903

The vasomotor studies of W T Porter alone and with his pupils[14] led him to results and views entirely antagonistic to those brought forward by Crile In the first place, in disagreement with Crile, he states that in his numerous experiments he failed to find an instance in which stimulation of an afferent nerve caused a significant fall of blood pressure, except, of course, on stimulation of a depressor nerve In his experiments, crushing or electric stimulation of the testis always gave a rise and not a fall of the blood pressure Continuous stimulation of the central ends of the sciatic, brachial or other afferent nerves for many hours gave uniformly the same rise of pressure as at the beginning An analysis of 765 blood pressure records from stimulations of the sciatic and brachial (and depressor) nerves of rabbits, cats and dogs brought out the result that the "percentage change in blood pressure, which is the true index of the condition of the vasomotor cells, increases as the blood pressure falls" Even in experiments where all the clinical signs of shock were present the blood pressure very low, the temperature subnormal, the heart beat weak and often irregular, and the irritability of the nervous system apparently much reduced, stimulation of the depressor nerve lowered the blood pressure by 45 per cent All these data, says Porter, are wholly opposed to the hypothesis that exhaustion of the vasomotor center brought on by over-stimulation can be the cause of surgical shock Porter offers no theory of his own as to the nature of shock, but he is very emphatic in his assertion that the vasomotor cells in shock are neither exhausted, depressed nor inhibited Porter contradicts Crile's facts and disagrees with his exhaustion theory, but apparently he also disagrees with Howell's views, that inhibition of the vasomotor and cardiac centers are at the bottom of the phenomena of shock

In connection with this review it may be mentioned that, according to a recent statement of Sollmann[15] and his associates, "corrosion or violent irritation of the gastric mucosa, submucosa and serosa, or of the parietal peritoneum has generally no effect on blood pressure or respiration in anesthetized dogs, the observations extending some time over an hour"

This brief review will suffice to show that the experimental era has not yet solved the mystery of shock, and that the bringing forward of new experimental facts capable of shedding some more light on our puzzling problem is not yet a superfluous luxury Before beginning the report of our own experimental results I wish to complete the foregoing review by the addition of two brief statements

14 Porter W T Am Jour Physiol 1907-'08 xx pp 399 444 and 500
15 Sollmann, Brown and Williams Am Jour Physiol 1907 xx p 74

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11 Boise   Amer Jour Obstet , 1907, lv, p 1

12 Malcolm   Lancet, Aug 26 1905, ii, also Lancet 1907, i, p 497

13 Howell, W H   Contributions to Medical Research, dedicated to Victor C Vaughan, 1903

The vasomotor studies of W T Porter alone and with his pupils[14] led him to results and views entirely antagonistic to those brought forward by Crile In the first place, in disagreement with Crile, he states that in his numerous experiments he failed to find an instance in which stimulation of an afferent nerve caused a significant fall of blood pressure, except, of course, on stimulation of a depressor nerve In his experiments, crushing or electric stimulation of the testis always gave a rise and not a fall of the blood pressure Continuous stimulation of the central ends of the sciatic, brachial or other afferent nerves for many hours gave uniformly the same rise of pressure as at the beginning An analysis of 765 blood pressure records from stimulations of the sciatic and brachial (and depressor) nerves of rabbits, cats and dogs brought out the result that the "percentage change in blood pressure, which is the true index of the condition of the vasomotor cells, increases as the blood pressure falls" Even in experiments where all the clinical signs of shock were present the blood pressure very low, the temperature subnormal, the heart beat weak and often irregular, and the irritability of the nervous system apparently much reduced, stimulation of the depressor nerve lowered the blood pressure by 45 per cent All these data, says Porter, are wholly opposed to the hypothesis that exhaustion of the vasomotor center brought on by over-stimulation can be the cause of surgical shock Porter offers no theory of his own as to the nature of shock, but he is very emphatic in his assertion that the vasomotor cells in shock are neither exhausted, depressed nor inhibited Porter contradicts Crile's facts and disagrees with his exhaustion theory, but apparently he also disagrees with Howell's views, that inhibition of the vasomotor and cardiac centers are at the bottom of the phenomena of shock

In connection with this review it may be mentioned that, according to a recent statement of Sollmann[15] and his associates, "corrosion or violent irritation of the gastric mucosa, submucosa and serosa, or of the parietal peritoneum has generally no effect on blood pressure or respiration in anesthetized dogs, the observations extending some time over an hour "

This brief review will suffice to show that the experimental era has not yet solved the mystery of shock, and that the bringing forward of new experimental facts capable of shedding some more light on our puzzling problem is not yet a superfluous luxury Before beginning the report of our own experimental results I wish to complete the foregoing review by the addition of two brief statements

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14 Porter W T   Am Jour Physiol 1907- 08 xx pp 399 444 and 500
15 Sollman Brown and Williams Am Jour Physiol 1907 xx p 74

Henderson[16] has recently adopted Mosso's theory of acapnia also for the causation of shock Acapnia means an insufficiency of carbon dioxid in the tissues and fluids of the body, and Mosso believes that this insufficiency is the cause of mountain disease Henderson believes that the lack of carbon dioxid is also the cause of shock which, for instance, develops in laparotomies on account of the escape of this gas from the exposed peritoneum and intestines

The other statement has reference to the brief mention of Bainbridge and Parkinson[17] last year of two autopsies of postoperative shock in which the chromaffine tissue of the suprarenals was absent If such findings should turn out to be the rule, we may soon find a new and plausible theory of the nature of shock This, however, must be left to the future

Our experiments which I wish to mention here were not undertaken and carried out with a view of determining the nature of shock Laparotomies were made on animals under various conditions for the purpose of studying certain problems in connection with the gastrointestinal canal In these studies, however, some facts came to light which may be of assistance in the elucidation of some of the mysteries of shock, and that is the reason why I wish to report them here

The first series of experiments deals with the motility of the gastrointestinal canal We found there the fact that simple opening of the abdomen has a profound influence on this motility Experimenters open the abdomen as one opens the door of a room to see the doings and hear the conversation which is going on, and they are then surprised that everything is quiet If the abdomen of a rabbit is open it is found that the bulky organs, the stomach and cecum, which fill up nearly the entire abdominal cavity, are practically without any motion

The literature, therefore, contains hardly any statement concerning the motility of these organs, especially that of the cecum, which is very large in the rabbit Dr Auer and myself[18] have discovered, however, that if a normal rabbit is stretched out on its back and the hair over the abdomen cut the regular movements of the stomach and cecum are very plainly visible, the movements of the cecum are especially coarse and easily visible and palpable Nevertheless, on opening the abdomen there is not a sign of these movements, which appear to be suppressed by this procedure

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16 Henderson, Yandell Am Jour Physiol, 1908, XXI, p 126
17. Bainbridge and Parkinson Lancet, 1907, i, p 1269
18 Meltzer and Auer Zentralbl f Physiol, 1907, XXI, No 3, Proc Soc for Exper Biol and Med, 1907 iv, p 37, also John Auer Am Jour Physiol, 1907, XVIII, p 347

We then carried out a series of experiments to find out the cause and nature of this suppression The cecum was studied first In the beginning we sought to determine whether it is not the pain due to the incision after the animal comes out from the anesthesia which inhibits the movements For this purpose we have first sectioned the spinal cord at the upper end of the dorsal region Sooner or later the movements of the cecum were as regular as usual We could now open the abdomen without causing the animal any pain But it was found that now, too, there was not a sign of cecal movement The suppression, then, was not caused by pain The opening of the abdomen admits air, and sometimes cold air, and it is usually assumed that this has a profound effect on the peritoneum and intestines We thought that this might be the cause of the suppression of the movements In testing this surmise we discovered that it was not necessary to open the abdomen, simple free dissection of the skin of the abdomen from the underlying muscles was sufficient to stop these movements It was then evident that the suppression of the movements was not due to direct action upon the cecum but to some reflex act Temporary closing of the skin over the wound restored the movements again That it was not the contact of the skin area with the cold air or at least that it was not this alone, which caused reflexly the suppression of the movements could be proved by the fact that covering the area with warm physiologic solutions did not restore the movements A similar result was obtained, though the effect was less strong, when the skin of the thighs was freely dissected Furthermore, even submerging the posterior part of the animal with the cut cord in a bath of 40 degrees C stopped the cecal movements for some time Apparently any adequate stimulus applied to the animal caused by way of reflex to the spinal cord an inhibition of the cecal movements The dissection of the skin presents such a stimulus, and although we are as yet ignorant as to which of the factors accompanying the dissection is the essential stimulus, we know that the dissection presents a group of abnormal conditions, and any abnormal condition might serve as a stimulus The assumption that the suppression of the cecal peristalsis is an act of reflex inhibition we have further tested by the complete destruction of the spinal cord In this case dissection of the skin was incapable of interfering with the cecal peristalsis, which was then even better than before The evil ghosts of exhaustion and fatigue which for more than half a century cast their dark shadows on many bright ventures in physiology could not obscure the issue here The suppression of cecal peristalsis by dissection of the skin could not have been brought on by over-stimulation and exhaustion since after destruction of the cord and

dissection of the skin the peristalsis was not hampered and in fact was better than before. The mechanism of this reflex inhibition of peristalsis is apparently this. The splanchnic nerves and perhaps also some hypogastric nerve fibers are inhibitory nerves for the gastrointestinal canal, just as the vagus is an inhibitory nerve for the heart. In the normal state an inhibitory tonus is present, that is, cutting of the splanchnic nerves causes an increase of the normal peristalsis. The tonus is probably sustained by continuous mild reflex stimulation from the periphery. When an abnormal, strong stimulus is applied to the periphery, like the dissection of the skin, reflex inhibition becomes increased to such a degree as to completely stop the normal peristalsis. When, however, the cord is destroyed and no spinal reflexes are possible, the dissection has no effect and by the elimination of the normal tonus the normal peristalsis becomes even greater.

Our further experimentation, however, revealed the presence of another inhibitory mechanism. We found that after destruction of the cord there was a sharp difference in the effect between simple dissection of the skin and complete opening of the abdomen. In the latter case the peristalsis, which now did not disappear immediately after the performance of the laparotomy, was not as complete as normally and continued only for a short time. Even in a warm bath of a physiologic solution the cecal peristalsis ceased after ten or fifteen minutes. Since there could be no reflex effect, the early subsidence of the movements must have been accomplished by the stimulation of some peripheral inhibitory mechanism. We did not try to locate the habitat of this mechanism, whether it be in the peripheral ganglia, nerve endings or within the muscle cells of the intestines.

This series of experiments, then, established safely the following conclusions. That simple dissection of the skin over the abdomen presents a distinct stimulus; that this stimulus when the corresponding part of the spinal cord is intact causes a reflex of an undoubted inhibitory character; when the cord is destroyed the opening of the abdomen brings on a stimulation of peripheral inhibitory mechanisms and that, therefore when the cord is intact the opening of the abdomen is instrumental in bringing out a two-fold inhibition—a reflex inhibition and an inhibition of a local peripheral mechanism.

These conclusions found their verification in results at which Cannon and Murphy[19] arrived in a series of different experiments. Cannon as is well known studies the movements of the gastrointestinal canal in

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19 Cannon and Murphy. Jour Am Med Assn 1907, xlix p 840

normal animals by the fluoroscopic method   In a series of experiments which he carried out together with F T Murphy it was found that crushing the testes of cats under anesthesia stops the peristaltic movements of the small intestines   When the splanchnic nerves were previously cut, however, the crushing of the testes did not interfere with the movements of the intestines   This shows that the crushing of the testes presents a stimulus which causes reflex inhibition of the intestinal peristalsis   Furthermore, Cannon and Murphy found that the transportation of food from the stomach through the intestines, which in cats does not stop by simple exposure of the intestines to the air, is greatly inhibited when the intestines are handled within the abdominal cavity and still more so when they are removed outside of the cavity and handled there   To test the nature of this inhibition Cannon and Murphy repeated these experiments in animals whose splanchnic nerves were previously cut   It was found that the handling still inhibits the movements   The inhibition called forth by the handling, therefore, is due to some local mechanism   Here again we have two varieties of inhibition —reflex inhibition and local inhibition of peripheral origin

Before discussing the bearing of these facts upon the question of the nature of shock we shall first record some other observations brought to light by the investigations of Dr Kast and myself in a series of experimental studies of the sensibility of the gastro-intestinal canal

As is now well known, the observations made in human laparotomies under local anesthesia led the surgeons to the view that the abdominal viscera feel no pain and possess no sensory nerve fibers   In an extensive study which we made on dogs we found that the intestines are sensitive enough as long as they remain within the abdominal cavity and are very little or not at all exposed to the air   When the abdomen is freely opened and the intestines removed from the cavity the sensibility becomes greatly reduced or entirely abolished temporarily or even permanently   It is with sensibility the same as with motility, the sudden opening of the abdomen is like the sudden opening of a door which throws a hush on the lively company inside of the room   When the abdomen was opened under anesthesia and one loop of intestine was gently fixed between the branches of a dressing forceps and the abdomen then closed with temporary sutures   any moderate pressure on the protruding handle of the forceps invariably called forth an unmistakable sign of the sensation of pain   The result would remain constant for hours   If, however, all the temporary sutures were opened at once and stomach and intestines permitted to escape from the abdominal cavity,

in a minute or two the sensations of the intestines would be greatly reduced or completely abolished and would remain so for a shorter or longer period until the intestines were returned to the abdominal cavity and the abdomen closed or at least kept well covered with warm physiologic solution We shall not enter here, of course, into any details of these experiments We wish, however, to call attention to the following accompanying circumstances Simultaneously with the loss of intestinal sensibility a distinct reduction of the sensitiveness of the skin over the entire body takes place, and at the same time the animal becomes distinctly apathetic The dog, which a few minutes before was whining and restless, suddenly becomes perfectly quiet and strikingly indifferent, although the eyes are wide open and the lid reflex is active A strong stimulus applied to the skin would wake up the animal, but only to sink again into the lethargic condition The intestinal and skin insensibility and the general apathy set in even if the opening of the abdomen occurred in a warm bath of saline or Ringer's solution The reduction of the sensibility of the skin is as a rule less pronounced than that of the intestines, the sensitiveness of the skin returns also a good deal sooner The general apathy lasts a good deal longer During all this time the blood pressure remains high, it may be as high as 150 millimeters of mercury or even higher The pulse, which sometimes becomes rapid for a short time, soon returns to normal, and the respiration may be even slower than normally

What does this loss of sensibility and apathy mean? With high pressure the phenomena can not be due to anemia, and with normal pulse, normal pressure and normal respiration it does not look like an exhaustion Knowing now that the suppression of the motor phenomena by the opening of the abdomen is surely an inhibitory effect, we assume that the blunting of sensation and perception also means an inhibition, that is, an inhibition of the receptive sensory elements Furthermore, since the processes of the reduction of the sensation from the skin and of the general apathy can take place only within the central organ, we have reason to assume that the stimulating factors combined with the opening of the abdomen create at the central end of the sensory nerves inhibitory processes which are responsible for the phenomena above described

For reasons into a discussion of which we do not wish to enter here, we consider it possible that in the nerve fibers of the intestines the peripheral receptive endings might also become somewhat affected by the opening of the abdomen At any rate the sensitiveness of the intes-

tines was distinctly more reduced than that of the trunks of the mesen-
teric nerves

We may mention here an observation made by Dr Auer and myself
in studies upon the respiratory vagus Although these studies are far
from complete, the one fact which interests us here stands out quite
clearly It has been known for half a century that stimulation of the
central end of a vagus nerve, especially in rabbits, affects the respiration
so as to cause a standstill Numerous investigations were made on this
subject and there has been a contention among the various writers
whether the standstill occurs in inspiration or in expiration Standstill
in inspiration means a tetanic contraction of the diaphragm, and stand-
still in expiration means an inhibition of the spontaneous contractions
of the diaphragm The inhibition occurs within the medulla oblongata
and is of the same nature as the inhibition produced by the stimulation
of the central end of the superior laryngeal nerve Some years ago I[20]
showed that both statements are true, namely, that in some animals stim-
ulation of the vagus causes standstill in inspiration, in others standstill
in expiration This means that the vagus contains two kinds of nerve
fibers—stimulation of one kind causes excitation, that is, inspiration, and
stimulation of the other causes inhibition of inspiration Which of the
effects prevails depends in each particular case upon conditions which
are as yet unknown to us We have now observed in a few dogs and
rabbits that after the abdomen is widely opened stimulation of the cen-
tral end of the vagus causes invariably an inhibition of inspiration This
means that the opening of the abdomen contains elements which favor
the predominance within the medulla of an inhibitory state for the res-
piration We may add that in these experiments, too, it was evident that
the opening of the abdomen is the cause of a manifest reduction of the
sensibility of the skin

Turning again to our experiments on the sensibility of the abdominal
organs, we have to point out a few more facts which are of special in-
terest to our problem In many of our dogs, especially in vigorous
animals, blood pressure, pulse and respiration would remain normal for
many hours, in fact the experiment had to be broken off before there
was any sign of a so-called vascular shock Meanwhile the viscera had
been repeatedly eventrated and replaced in the abdominal cavity, the
animal becoming more and more insensible to any stimulation and deeply
apathetic while the blood pressure never was less than at least 100
millimeters mercury In other animals the blood pressure dropped

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20 Meltzer Arch f Physiol , 1892, p 340

within two or three hours to 60 or 50 millimeters, the pulse ran up to about 180, the respiration was irregular and otherwise the animal presented the picture of deep shock   Again, in another comparatively small group of animals it came to pass that immediately after a sudden release of the temporary ligatures of the abdomen the animal sank into a state of deep shock   It lay absolutely motionless as if paralyzed, no manner of stimulation of the skin would bring out any reaction, the eyes were half closed with a completely indifferent look, though the lid reflex was not entirely abolished   The respiration was very slow and gasping, the pulse very rapid and small, although the blood pressure was still 70 or 60   The mucous membranes were usually pale, the viscera showing at least no hyperemia   The blood was always dark   All this would occur even when the opening of the abdomen took place in a bath of 40 degrees C   The animals of this group were far from vigorous, of a meek temperament and not well nourished   Even these animals did not die spontaneously, they were usually killed by clamping the trachea or by putting the tracheotomy tube under water, and the remarkable fact was then noted that in these animals the asphyxia did not result in any convulsions

The shock seen in these few animals had a remarkable similarity to traumatic shock as described by Fischer and others in the human being, although in two of these animals the blood pressure was not lower than 60 millimeters

From this series of experiments we have learned the following facts which have a bearing upon our problem   In all experiments in which our attention has been directed toward this point, opening of the abdomen and evisceration led invariably to a reduction of the sensibility of the skin and to general apathy, from both of which the animal is apt to recover sooner or later when the viscera are properly taken care of   While both of these conditions may attain sometimes a considerable degree of intensity, the heart and blood pressure may remain entirely unaffected   If the tough handling of the abdominal viscera continues, the insensibility and the general apathy increase   In vigorous animals this did not readily lead to a surrender of the functions of the body to complete shock so that even after many hours of exposure and handling, blood pressure, heart and respiration still had suffered little   In less vigorous animals also the last named functions gradually surrendered to the effects of continuous rough handling of the viscera, these animals gradually sank into complete shock   Finally in animals with reduced bodily resistance complete shock appeared soon after laparotomy and evisceration.

In some cases an undoubted profound shock was present, although the blood pressure was not lower than 70 or 60 millimeters, a degree of pressure which, if not complicated by any other ill conditions. is still far away from the danger line

We wish to point out especially that in our experiments in the cases in which the development of shock was gradual the symptoms of insensibility, general apathy and complete muscular relaxation invariably made their appearance long before the onset of cardiac and vascular breakdown

Before continuing the discussion of our experiments further, I wish to make the following remark with reference to the symptoms of shock In the above reported recent literature on shock low blood pressure is the paramount symptom, possibly also a rapid pulse In the lucid description of traumatic shock of some of the older writers blood pressure was represented only by the few words that the arteries were of low tension, while there was a great deal to say about the peculiar mental state, the insensibility, the immobility, the respiration, etc I may also mention here that in referring to Goltz's experiments on the effects of stroking the abdomen of frogs, usually only the condition of the heart and blood vessels is taken into consideration, while Goltz has expressly pointed out that as long as the animal is under the influence of the stroke reflex it is as if paralyzed and seems to be without sensation Painting the leg with acid causes no reaction, later, when the animal recovers, it tries to get rid of the irritant I emphasize these points to show that the symptoms of general apathy, of insensibility and of muscular weakness are integral symptoms of shock The recent experimental studies on blood pressure in shock have, I believe, in some respects obscured the issue Low blood pressure is surely one of the symptoms of shock, but it is not the only symptom Again, it is not necessary in the definition of shock to assume the presence of blood pressure so low that the animals can not recover, as there is sufficient clinical evidence that recovery from shock may occur Furthermore, there may be fatal shock without a very low blood pressure, and there may be very low blood pressure without the condition of shock.

While I do not wish to enter here into a detailed discussion of diagnosis, it seems to me quite safe to state that for the diagnosis of traumatic as well as surgical shock it is necessary to take into consideration the general mental state the states of the sensibility and motility and the conditions of the cardiac, vascular and respiratory functions

Returning again to our own experiments, we have seen that in animals of all degrees of vitality laparotomy and handling of the intes-

tines leads to some degree of general apathy, insensibility and motor relaxation, in other words, to some of the symptoms of shock This partial shock is not necessarily fatal and concerns functions which are not of immediate vital importance With the prolongation of the exposure and handling of the viscera, the danger of the involvement of the cardiac, vascular and respiratory functions increases, and the danger is the greater the lower the vital resistance of the animal The last-named functions are of greater importance for the continuation of life and are, therefore, in the vigorous animal provided with greater factors of safety, so that minor assaults do not easily shake their foundation

Generalizing our experience, we may say that the sudden opening of any body cavity will frequently cause a partial shock which may consist of the anesthetic condition of the contents of this cavity, a reduction of general sensibility and a general muscular relaxation When the handling of the contents of the cavity is continued and the powers of resistance of the subject are at a low point, a more or less complete shock develops, in which other more vital functions become involved in varying degree sometimes the heart, sometimes the vascular system, and sometimes the respiratory mechanism, are predominantly affected Similar conditions may be brought on by extensive dissections or burning of some parts of the body, it should be borne in mind that one part may perhaps react more readily than another Beside these intentionally produced or accidental injuries, violent mechanical agitation of some especially sensitive part without actual destruction of tissue might also be capable of calling forth more or less complete forms of shock All these various methods of producing partial or complete shock represent in one form or another strong stimulations abruptly applied to the normally tranquil nervous system

What is the nature of that condition which we term shock? We are in the habit of expecting a stimulus to produce or increase an activity In shock the activity of the functions is depressed or suspended By what method do the stimulating injuries cause this depression or suspension of activity? The current view is that the depression is a state of exhaustion or fatigue of the functions or of the nerve cells controlling them In estimating the value of this hypothesis, one should remember that it was first advanced to account for the inhibitory effect of the vagus upon the heart The objectors to the new idea of inhibition tried to explain the fact of the arrest of the heart's action by assuming that the vagus was the motor nerve of the heart, and that the cutting of the nerve caused fatigue of the heart by overstimulation

Since this time this has been the favoite hypothesis of some writeis to explain any ieduction of activity of the nervous system   The fact that no hyperactivity of the function piecedes its depiession does not seem to have any weight with these writers

In our own experiments upon the motility of the gastiointestinal canal we have seen that the dissection of the skin produced a suspension of the normal movements which could not depend on fatigue and exhaustion, since the destruction of the cord iestored the function of the gut to even greater activity   It was evident that in this case the dissection of the skin gave rise to an inhibition of the motor function of the gastrointestinal canal similar in chaiacter to that of the cardiac inhibition   Furthermore, in the studies of the effects of the stimulation of the vagus on respiration, it was found that opening of the abdomen favoied the inhibitory response to stimulation to the central end of that nerve   These facts demonstrate that dissections of the skin oi opening of the abdominal cavity do not produce exhaustion, but result in a moie active inhibition

On the other hand, Howell has called attention to the fact that the vascular depression in shock is not preceded by increased activity sufficient to justify the assumption of exhaustion from over-stimulation of the centei   Furthermore, in the stioke experiments of Goltz, the geneial paialysis and the anesthesia prevalent during the stioking of the abdomen is never preceded by tetanus or hyperesthesia

On the basis of these considerations I venture the assumption, which is not new, that the vaiious injuries which are capable of bringing on shock, do so by favoiing the development of the inhibitoiy side of all the functions of the body   This predominance of inhibition makes its appeaiance at fiist in those functions which aie of less immediate impoitancc to life, and are, therefoie, less insured by safeguaids protecting their equilibiium   With increased injury the inhibition spreads also to the moie vital and, therefore, bettei protected functions of the nervous system   The eaily inhibition in the development of shock, of the functions of lessei impoitance, might even be looked on as being, in a degiee, conseivative measures of protection of other moie important functions of animal life   The iestfulness of the body, the painlessness and mental indiffeience aie certainly most desirable conditions in the management of shock oi the moie vital functions

We shall say here a few woids as to the meaning and impoitance of inhibition in connection with oui pioblem   The body's functions aie eleaily constructed on the dual principle   The heart has the acceleratois as motoi and the vagi as inhibitoiy neives   The vasculai system has

in the centrifugal direction vasoconstrictors and vasodilators, the latter having simply inhibitory functions   In the centripetal direction there are nerve fibers which increase the tonus of the vasomotor center, as the fibers within the sciatic nerve, and there are nerve fibers which inhibit and depress the tonus, as the depressor nerve   For the respiratory centers there are fibers which augment inspiration, as certain fibers in the vagus, and others, as the superior laryngeal nerve, which inhibit inspiration   The same holds good for expiration   For the gastrointestinal canal the vagus is essentially a motor nerve and the splanchnic nerve essentially an inhibitor   These instances will suffice to support the contention that the functions are not kept up simply by acting when there is a stimulus to them and by resting when a stimulus is lacking   They are, on the contrary, constructed on the dual principle, on a well-balanced antagonism between excitation and inhibition   During life there is never an absence of stimuli, they stream continually in legions from outside and are ever present in the blood and lymph   The normal state of a function results from a proper balance of antagonistic stimulations, and the important functions are well provided with factors of safety to keep up the normal equilibrium

Under unusual abnormal conditions, however, there may arise a tendency toward a deviation in one or the other direction, that is, in the direction of excitation or in that of inhibition   With regard to shock, our theory assumes that the injuries which produce shock disturb the equilibrium, causing a tendency toward inhibition   It certainly does not mean reducing the function to a single principle, to inhibition alone, it only means shifting the tendency toward inhibition   Stimulation of nerve fibers which usually cause excitation will still cite, and fibers which cause inhibition will still inhibit and probably inhibit even better than in a normal state   Porter's experiments showing that in shock the depressor is very active, more so even, than when the blood pressure is normal, is far from being evidence against the theory that in shock the vasomotor center is more favorable toward inhibition, on the contrary it would tend to support this idea

The assumption that the insufficient activity of several functions during shock is due to a preponderating inhibitory influence refers only to the primary effect   It seems to me self-evident that during the course of shock other influences must become secondarily active   The insufficient activity of one function becomes detrimental to the other, and anemia asphyxia or even fatigue or other conditions might become operative during the progress of shock

Rockefeller Institute for Medical Research

CHLOROFORM NECROSIS OF THE LIVER

H GIDEON WELLS, M D

CHICAGO

The occurrence of serious, frequently fatal, poisoning as a sequel of chloroform anesthesia, manifesting itself first several hours or even a few days after the use of the drug, has been brought into prominence through the articles of Ballin, Bevan and Favill, Brewer, Brackett and others in this country, and of Guthrie in England, therefore, it is unnecessary for me to discuss the literature at length, as this will be found fully abstracted to 1905 in the article of Bevan and Favill,[1] and subsequent articles are indexed in the foot notes to this article

REPORT OF THE CASE

I desire merely to report a study of both the pathologic anatomy and the chemistry of a typical case, which I had the opportunity of examining at autopsy, through the courtesy of Dr F S Tufts, and to consider certain features illustrated by this case and those so far recorded in the literature   Dr Tufts has kindly furnished me the clinical history, which follows

Clinical History—"The patient, a vigorous young man, was born in Wisconsin in 1878   The family history is negative   He came to Chicago in 1899, and has been employed as a foreman in the hog-casing department of a packing house   In 1900 he married a first cousin, who gave birth to a healthy boy in 1904   His childhood history was negative, and up to 1902 he was strong, robust, and of very good color   In 1902 he lost weight and color, and began to complain of an occasional stomach trouble   He had no acute attacks or colic, but occasionally there was acute distress from gas after meals, with a sensation of fullness   The first acute attack of colic and cramps occurred on Jan 1, 1907, and was brought on by a hearty packing house restaurant dinner   I saw him two hours after the attack and found slight tenderness in the umbilical region, but nothing around or near the gall bladder   he returned to work the next day and was free from trouble until March 17   This second attack was apparently caused by fruit salad which he had eaten the day before   At this time I found no fever, some rigidity in the right rectus, but not much tenderness, he had had colic and cramps all night but not severe enough to call me   On the next day, March 18, he went to work, although still a little lame, and the following day visited me at my office when the gall bladder was found markedly distended, it extended 10 cm below the costal arch was freely movable and slightly tender   At this time there was no fever no icterus nor even bile in the urine (Gmelin s test)   On the next day his condition was about the same although the temperature was 99 2, pulse 78   The following day (March 21) the temperature was normal and the tenderness was

1 Bevan and Favill, Jour Am Med Ass'n 1905, xlv 691-696

subsiding, but he was quite pale and complained of feeling very weak, in the evening he was taken to the Englewood Hospital " Here his pulse, temperature and respiration were recorded as normal, and he was prepared for operation, which was performed at 4 p m on March 22

Anesthesia —The anesthetic was chloroform and it was "given with a free hand" by the anesthetizer, and cyanosis was very marked   The duration of anesthesia, however, was not long, as it is recorded that the patient left the ward for the operating room at 4 p m, returned at 5 p m, and was again conscious at 5 30 p m

Operation —When the abdomen was opened the upper surface of the liver was found freshly adherent to the parietal peritoneum, while the lower surface, gall bladder and intestines were bathed with lymph and fresh adhesions everywhere The gall bladder was thickened, but neither it nor the ducts were distended, and no stones could be palpated   On account of the evidently acute nature of the infection it was deemed wiser not to open the gall bladder, and the bad way in which the patient was taking the anesthetic impelled haste, so the abdomen was closed again without draining the gall bladder

Postoperative History —Following the operation the patient slept fairly well and the next day at noon the temperature rose to 99 7, but subsided on the following morning, March 24, although at this time there was a leucocytosis of 17,000   All this day the patient was in good condition, sleeping much of the time, until 11 p m, fifty-five hours after the operation, when he began to be restless   By 3 a m, March 25, he began to be delirious, acutely maniacal, and was unconscious from that time on, although he could be roused somewhat by calling   On the morning of this day the temperature at 10 30 was 99 3, pulse 82, respiration 22   The patient was very thirsty, icterus began to appear, and the urine, which before the operation had been normal, now showed much bile, albumin and hyalin and granular casts, but no crystals of leucin or tyrosin could be found   Under the influence of chloral and bromids the patient became more quiet at about 4 p m, laughter and crying taking the place of the wild delirium previously exhibited   The jaundice had increased during the day   By 3 p m the temperature had risen to 103, at 5 p m it was 104, at 7 p m, 106, and at 8 p m, 107   Death occurred at 9 30 p m, 100 hours after the operation

Autopsy —This was performed at 9 o'clock the next morning, in the undertaker s room, to which the body had been removed   An attempt at embalming with an arsenical solution had been made just before our arrival, but fortunately this was so ineffectually done that practically none of the fluid penetrated the viscera and they were almost unaffected, however, there had been some fluid introduced directly into the peritoneal cavity, which interfered with cultures being made from the peritoneal exudate and gall bladder, while of course blood cultures were made valueless by the intravascular injection

Autopsy Report —This is summarized below

Anatomic Diagnosis   Acute hepatic degeneration and atrophy   Cholelithiasis with chronic suppurative and proliferative cholecystitis   Acute fibrinous pericholecystitis   Suppurative cholangitis with fibrous pericholangitis   Partial occlusion of cystic duct near juncture with hepatic duct   Recent operative incision in right hypochondrium   General icterus   Multiple ecchymoses in serosa of thoracic and abdominal cavities   Hypostatic pulmonary congestion   Right inguinal hernia

External Appearance   Young man, slenderly built, fairly nourished, very icteric all over the body, especially the face, sclera bright yellow   Scar of old trauma over right tibia   Recent operative incision three inches long in right hypochondrium, also embalmer's incision in right arm   Discolored skin areas from saline transfusion over both pectorals   Right inguinal canal open a short distance

Abdominal Cavity Distended by clear embalming fluid (arsenic and bichlorid of mercury) (Clinically it was flaccid up to death) Omentum free Numerous small blood extravasations throughout omentum Many hemorrhagic foci, size of pea and smaller, scattered throughout mesentery and retroperitoneal tissue Several larger suggillations more sparsely distributed Appendix free, three inches long, no mesoappendix, no changes

Gall Bladder Adherent to colon and pylorus by fresh, easily torn, fibrinous adhesions Surface of gall bladder covered by fibrin, beneath which are numerous hemorrhagic extravasations into the subperitoneal tissues Gall bladder wall greatly thickened, about 5 to 8 mm thick On palpation the bladder apparently semi-solid, cystic duct thickened and distended Lesser peritoneal cavity free Diaphragm at fourth rib on both sides Slight adhesions about spleen

Chest The entire mediastinal tissue riddled by ecchymoses, averaging about the size of a pinhead Pericardium studded with the same Pericardial cavity normal Both pleural sacs free from adhesions Pleura everywhere studded with small ecchymoses

Heart and Great Vessels Normal Portal system free from thrombi

Lungs Posterior parts of each lung congested and darker than the anterior and contain much fluid (Probably part is embalmer's fluid, no clinical indication of edema before death)

Liver This is small weight 1,050 g The margin is two fingers' breadth above costal margin The right lobe has been superficially hardened by embalming fluid The left lobe is not hardened to any extent The latter is very flabby, pinkish gray in color and looks almost as if decomposed The anterior margin is very sharp Surface discolored to a dirty pinkish-gray color and somewhat wrinkled The right lobe shows the lobular marks with unusual distinctness on the external surface as a fine network of lighter gray lines with reddish hexagonal areas between The cut surface of the right lobe shows the same mottling as seen externally, and is of a light yellow tinge The left lobe is very distinctly yellow, the lobular markings are difficult to distinguish The consistence is very flabby so that the liver can be folded upon itself The bile ducts and large vessels show no evident changes On pressure on ductus choledochus, a purulent yellow fluid exudes into the duodenum from the ampulla of Vater On incision of gall bladder a yellow muco-pus escapes In the bladder are over 100 stones, black hard, varying in size from 3 mm in diameter down to that of the finest sand The gall bladder wall is 6 mm thick There is nearly total obstruction of cystic duct near its junction with the hepatic duct by a fibrous occlusion (scar tissue) and pressure of a mass of recent fibrous tissue about the duct The hepatic duct seems to be normal A few stones occur in the ductus choledochus The latter shows an inflammation and swelling of the mucosa

Spleen Apparently normal Very much hardened by embalming fluid

Pancreas No evidence of fat necrosis and no other change observed

Kidneys Somewhat hardened by embalming fluid Normal size Capsule strips normally, no evident pathologic alterations

Adrenals Normal

*Histologic Findings —*Liver There is not a normal liver cell to be found, and very few indeed that are not totally necrotic At first glance the liver resembles an organ that has undergone extensive postmortem decomposition but it is soon seen that only the parenchyma cells have beeen affected and that there are quantitative differences between the conditions in the center and periphery of the lobules The lobules are somewhat reduced in size and only at the very periphery of the lobules can there be found parenchyma cells that show any approach

to the normal structure, these cells are never more than one or two layers deep from the periportal tissue, and the best of them show cloudy swelling and fine granules of fat   Immediately next to these cells is a narrow zone, representing a width equal to two to ten liver cells, in which the cells consist of a mere mesh work of fat droplets with no cytoplasm remaining and only exceptionally a nucleus   In all the rest of the lobule, which part constitutes from two thirds to four-fifths of the entire radius of each lobule, is total necrosis of the liver cells, nothing remains of them but the dead bodies of the cells, deeply stained by eosin and evidently greatly reduced both in size and number   There is no thrombosis in the hepatic capillaries, no acute or chronic inflammation, and no evidence of alteration in the bile ducts   By sudan III the necrotic central cells are found rarely to contain small fat droplets, although between them can be found Kupfer cells that are quite fatty   The vacuolated zone near the periphery is composed of cells containing large amounts of fat, and the most normal peripheral cells show numerous fat droplets

Kidney   Epithelium of convoluted tubules is granular and many of the tubules are swollen shut, and some contain occasional fat droplets, these are especially numerous in the straight collecting tubules   Some of the epithelial cells seem to be necrotic   The glomeruli contain a considerable amount of granular debris, but otherwise no changes   There is no hemorrhage, acute inflammation or connective tissue increase

Spleen, Myocardium and Pancreas   No changes found, except a small amount of fat in some of the muscle cells of the heart

Gall Bladder   Diffuse infiltration of the wall with lymphoid cells, plasma cells and some polymorphonuclear leucocytes

Chemical Examination of Liver —Immediately after the autopsy the liver was cut into thin slices, and 850 grams of the fresh tissue were placed in a large volume of 95 per cent alcohol until thoroughly hardened, and then subjected to chemical analysis, the details of which will be published elsewhere[2]   The chief results of this study may be summarized as follows   Among the water soluble substances obtained by extraction of the liver tissue were considerable quantities of free aminoacids, presumably derived from the proteins of the liver cells through autodigestion, of these aminoacids there were obtained in pure enough condition for identification 0 34 gram of histidin, 0 26 gram of tyrosin, 1 50 grams of leucin 1 57 grams of glycocoll and 0 58 grams of glutamic acid   The presence of arginin lysin, and pyrrolidin carbonic acid could not be definitely established, although there was obtained evidence which indicated that these substances were in the extracts   A further indication of the autolytic destruction of the liver proteins that was going on in this case was the finding of considerable quantities of proteoses peptones, and probably of polypeptids   Free xanthin and hypoxan thin were also found in the extracts, undoubtedly derived through autolytic disin tegration of the nucleoproteins of the liver cells   There was no increase in the gelatigenous substance of the liver, such as has been observed in acute yellow atrophy, since this is the result of regenerative proliferation of connective tissue, which had not begun to take place in the chloroform necrosis liver   The composi tion of the insoluble coagulated proteins left after thorough extraction of the liver with alcohol, ether, and cold and hot water was found to be quite the same in this liver as in two normal livers   at least so far as the form in which the nitrogen is bound   whereas a liver from a typical case of advanced acute yellow atrophy showed some loss of diamino nitrogen   This is shown in the following table giving the results of analyses of these four cases by Hausmann's method

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2 Wells H G   Jour Biol Chem 1908 vol v

COMPARISON BETWEEN ACUTE ATROPHY, NORMAL AND CHLOROFORM NECROSIS LIVERS

	Acute Atrophy	Normal (anemic)	Normal (congested)	Chloroform Necrosis
Amid nitrogen	5 5	3 7	4 8	3 9
Humus nitrogen	3 6	3 4	4 9	5 7
Diamino nitrogen	26 2	32 8	30 0	30 0
Monamino nitrogen	64 8	60 3	60 2	60 3

This same insoluble residue, which consisted chiefly of proteins, contained the same amount of sulphur as normal liver extracted under the same conditions The amount of iron was slightly increased, presumably because the hemolysis that always occurs in jaundice sets free iron-containing pigment which the liver stores up Phosphorus was found increased by three or four times the amount found in normal livers, and this in spite of the great destruction of nuclei that had taken place No satisfactory explanation for this increased amount of phosphorus has been found

There was found 72 4 per cent of water in this liver, 8 per cent of fats and lipoids and 18 8 per cent of dry, fat-free solids, which is somewhat different from the proportions found in typical acute yellow atrophy, as shown by the following table

	Water	Fat	Fat-free Dried Substane
Normal liver (Quincke)	76 1	3 0	20 9
Normal liver (Wells)	77 6	5 0	17 4
Acute atrophy (Perls)	81 6	8 7	9 7
Acute atrophy (Perls)	76 9	7 6	15 5
Acute atrophy (v Starck)	80 5	4 2	15 5
Acute atrophy (Taylor)	85 8	2 0	12 2
Acute atrophy (Wakeman)	79 3		
Acute atrophy (Wells)	83 8	2 5	13 7
Acute atrophy (Voegtlin)	78 0	6 6	15 4
Phosphorus poisoning (v Starck)	60 0	29 8	10 0
Fatty degeneration (v Starck)	64 0	25 0	11 0
Chloroform necrosis (Wells)	72 4	8 8	18 8

In respect to the amount of water, this chloroform necrosis liver stands between the typical acute yellow atrophy liver and the ordinary fatty liver, just as it does in its histology, that is, there has been some replacement of water by fat, as in the fatty livers but not so much replacement of protein by water as in typical acute yellow atrophy These figures emphasize the fact that in chloroform necrosis the amount of fat is distinctly increased, although not so much is found on analysis as might be expected from the microscopic findings Taylor states that, in the chloroform necrosis liver which he examined there were 200 grams of fat, which would be about twice the proportion that was found in my case, unfortunately he has not published sufficient details of the analysis to furnish the accurate information desired

The amount of lecithin and cholesterin in this case was found to be not greatly different from that present in normal livers, and thus again in marked contrast to the liver in acute yellow atrophy, as seen by the accompanying table

While the total amount of lecithin has decreased, this is only in proportion to the decrease in the total size and weight of the liver, this proportional decrease has gone on in spite of a relative increase in the amount of simple fat, showing the same lack of correlation between the lecithin and the neutral fat which has been observed by others who have determined the lecithin content of organs showing fatty degeneration Evidently, therefore the increase in the fat content of the liver in chloroform necrosis is due entirely to neutral fats The cholesterin, on

the other hand, has apparently remained in about the normal amount, and has not decreased with the lecithin and proteins, this is quite what might be expected from what we know of the tendency of cholesterin, when liberated by degenerating cells, to remain at the place where it is formed

	Lecithin				Cholesterin			
	Normal (Anemic)	Normal (Congestion)	Chloroform Necrosis	Ac Atr	Normal (Anemic)	Normal (Congestion)	Chloroform Necrosis	Ac Atr
Fresh weight, per cent	1 6	1 4	1 5	0 45	0 26	0 37	0 52	0 3
Total dry weight, per cent	6 3	6 25	6 2	2 9	1 0	1 7	1 9	1 8
Dry, fat-free material, per cent	7 7	8 0	8 1	3 2	1 25	2 1	2 9	2 1
Ether-soluble substances, per cent	35 3	28 0	17 3	17 6	5 7	7 4	5 9	11 1
Grams in entire liver	23 7	22 4	16 0	4 4	3 8	5 95	5 4	3 38

GENERAL CONSIDERATIONS

If we examine carefully the cases of "delayed chloroform poisoning," as reported in the literature under various titles, it becomes apparent that there are included two fairly distinct types of cases resulting from the same cause, and that these types differ both clinically and anatomically In one set the patient is usually a child, the clinical manifestations are vomiting, restlessness or extreme excitement, terminating in coma, frequently more or less cyanosis, and sometimes definite air hunger, a sweetish odor of the breath and acetone bodies present in the urine in most of the cases in which they were sought for, in other words, the symptoms resemble in many respects "acidemia" or "acetonemia,' under which titles many of these cases have been described The liver in these cases generally shows more or less fatty change, usually when described carefully the fat is said to have been chiefly in the periphery of the lobules, and there is no mention of necrosis of the hepatic cells in the published accounts of these cases Generally, fatty degeneration and more or less acute parenchymatous degeneration, sometimes even severe necrosis, are found to have taken place in the kidney In practically none of these cases has jaundice been observed, and the liver changes have not usually been very severe To this group belong all but perhaps one or two of the cases described by Guthrie, and the cases of Brackett, Brewer, and Telford and Falconer

Quite different from this group are the cases of Stoeckel, Bandler, Eilach Marthen Mintz Ballin Campbell-Horsfall, Guleke Cushing Taylor, Holmes and the one described in this report Here the clinical picture at first is rather similar to the first group, in that the onset is usually with restlessness, excitation, and delirium which passes into coma However in place of those symptoms which are usually considered as manifestations of acetonemia there appears a rapidly developing

jaundice, which toward the end is generally very severe   Associated with this jaundice are frequently observed cutaneous hemorrhages   The manifestations resemble in every respect a severe cholemia, associated in some cases with the finding of leucin and tyrosin crystals in the urine   Consequently several of these cases have been reported under the title of "acute yellow atrophy of the liver," which diagnosis is supported in the main by the anatomic findings at autopsy   The liver is usually decreased greatly in size, with wrinkled capsule, friable consistence, and yellowish or red and yellow discoloration, often the organ is so severely disorganized, as in the cases of Taylor and the one here reported, that it may be best described as "putty-like '   While there is always more or less fatty increase, this is usually more apparent than real, much of the yellow color commonly described as "fatty degeneration' being due to bile pigments, necrosis is the predominant change, beginning in the center of the lobules, as in typical "idiopathic" acute yellow atrophy

I have had the opportunity to study the histologic appearance of three typical cases of this kind including one that was reported by Dr Bayard Holmes[3] and, through the kindness of Dr Hektoen, the case reported by Drs Bevan and Favill, and the resemblance of the findings in all three is very striking.   As compared with the histologic picture described above in connection with the case which is the subject of this report the differences are but slight   The Holmes case differs only in having a slightly wider zone of well-preserved cells in the periphery and in the presence of more leucocytes, especially at the junction of the fatty and the necrotic zones   In the case of Bevan and Favill, which clinically was without jaundice or other evidence of hepatic involvement, the fatty zone is very much wider, and the necrotic central cells contain more numerous and larger fat droplets, the size of each lobule is, if anything increased rather than shrunken   But, taken all together, the histologic picture is strikingly similar in all three livers, practically identical in fact, and indicates the specificity of the effects of chloroform on the liver

This necrosis is associated with rapid autolysis of the dead cells, so that in my case the weight of the liver had fallen in four days to 1,050 grams, presumably from a normal weight of from 1 600 to 1 800 grams   As a result of this autolysis, leucin and tyrosin may appear in the urine and free amino-acids may be found in extracts from the liver itself   Of particular interest is the fact that in all the reported cases of this type as far as I can find the patients were adults, varying from 20 to 42 years of age, whereas, in the acetonemia type the patients were nearly all young children   The Bevan and Favill case in ' a girl aged 12½ years

3 Holmes Bayard Appendicitis 1904, p 214

with the stature of a woman," seems to lie at the border line between the two groups, for clinically there was no jaundice and the manifestations were of the "acetonemia" type, but histologically the liver, which was enlarged rather than shrunken, showed a considerable amount of central necrosis, although the fatty changes were more marked than in either of the other two cases that I have studied, and the necrosis and autolysis a little less extensive

Both sexes are represented in each type, with perhaps a slight preponderance of females   Why there should be this difference in the results of delayed chloroform poisoning in children and in adults I do not know, but the number of cases reported is too large to make it seem purely a matter of coincidence   Nearly all reported cases of fatal delayed chloroform poisoning seem to have occurred in the young, only two or three patients having reached the forties   Consequently there appears to be some difference in the liver or in the entire organism between youth and later life that determines this susceptibility to chloroform   In young adults the susceptibility of the liver seems to be particularly great, so that severe necrosis of this organ, with symptoms of hepatic insufficiency, dominates the anatomic and clinical picture

The changes in the liver, in this second type of delayed chloroform poisoning, are not essentially different from the changes in the early stages of acute yellow atrophy, except that there seems to be a more extensive fatty degeneration and infiltration   In true acute yellow atrophy there is no distinct increase in the proportion of fatty matter in the liver, while the total amount of fat is decreased more or less from the normal, along with the general loss of hepatic substance   In chloroform necrosis there is always more or less fatty metamorphosis noticed microscopically, and in the two cases in which the fat was extracted and weighed, Taylor's and my own, the amount of fat was distinctly increased above normal   It is possible that if one were to secure a liver in chloroform necrosis as long after the onset of the hepatic injury as is the case with acute yellow atrophy, where death occurs usually only after weeks rather than days, the changes might be found still more similar   for I have found that it is possible for a fatty liver to lose much of its fat and to have the fat replaced by fluid during the healing stages of the hepatic lesions produced by hydrazine poisoning [4]   However, even with this disparity of time   the results of analysis of a liver in idiopathic acute yellow atrophy of several weeks' duration are, on the whole very similar to those obtained with this chloroform necrosis liver,[5] and

4 Wells H G   Pathologic Anatomy of Hydrazine Poisoning, Jour Exper Med 1908 x No 4

5 Wells H G   Chemistry of the Liver in Acute Yellow Atrophy, Jour Exper Med , 1907, ix 627

I can not take issue with those who have diagnosed their cases of delayed chloroform necrosis as acute yellow atrophy Nevertheless. I believe that it would be well to reserve this term for those cases of hepatic atrophy which occur without evident cause, and which are characterized by a widespread necrosis of the liver cells without fatty metamorphosis, followed by rapid autolysis and removal of the necrotic cells, and early proliferative activity of the interstitial tissues and the bile duct epithelium As a particular characteristic of this disease should be mentioned the fact that the organs other than the liver seem scarcely to suffer at all or only secondarily to the hepatic insufficiency Chloroform necrosis, puerperal eclampsia, and certain violent septicemias, produce changes in the liver that are more or less similar to those described above, but never quite the same, especially in the relatively great injury of other organs and the extent of fatty changes in the liver, therefore, I believe that we would do best to refer to these several forms of hepatic necrosis by the names of the condition causing them, considering the typical "idiopathic acute yellow atrophy" as a pathologic entity, which perhaps may be found to have a specific cause

As to the reason for the severe effects that chloroform sometimes produces on the liver, some time ago I advanced a hypothesis somewhat as follows [c]

Chloroform is a protoplasmic poison for cells of all kinds, stopping their synthetic activities but not seriously impairing their autolytic enzymes This we see if we add chloroform to a culture or emulsion of bacteria, the cells at once die and begin to undergo autolysis In view of the nature of the changes that occur in the liver in chloroform necrosis it seems probable that a similar effect has been produced by the chloroform upon the liver cells, that is, their synthetic activities are checked, and autolysis goes on unbalanced by constructive processes Presumably it is the oxidative enzymes that are chiefly affected by chloroform, for, if these were destroyed, the resulting changes would be exactly what we observe taking place in chloroform necrosis, that is, the lipase would act unbalanced by the normal oxidative destruction of fatty acid and glycerin and so fat would accumulate in the cell, while at the same time synthetic changes, which seem to depend upon oxidative processes and the correlated reductions, would be stopped, and autolysis would assume the upper hand While at the present time we have no means of determining the correctness of this hypothesis, still it can be said that nothing that is not in harmony with this theorization has yet been learned concerning the processes that take place in chloroform necrosis Chemical analysis has merely corroborated the anatomic evidence of autolysis and fat increase in the liver cells

Just why the liver should only occasionally suffer this serious injury from chloroform is still unexplained Although in my own case it is probable that excessively free administration of chloroform may have been of influence in many of the recorded cases this explanation has not been available for often it is stated specifically that only a small amount

c Wells H G Delayed Chloroform Poisoning and Allied Conditions Jour Am Med Ass'n Feb 3 1906 xlvi 341

of chloroform has been used There is abundant evidence that anything that impairs oxidation favors the occurrence of chloroform poisoning, and diseases that are prone to affect the liver, especially those that of themselves frequently cause fatty changes in the liver, are said, by all who have studied delayed chloroform poisoning, to be important predisposing factors As a possible explanation of this apparent relation of pre-existing fatty changes in the liver to chloroform necrosis of the same organ, I would make the following suggestion

Chloroform, like other anesthetics, seems to owe its effect on the nervous system to the fact that it is a strong fat solvent, and hence is taken up by the lipoids of the nervous tissues This fact was first brought out by Overton and Meyer The amount of chloroform that a tissue will take up, therefore, depends on the amount of fatty material in it which can dissolve the chloroform out of the blood, this is on the same principle as the method used in the laboratory for separating substances of different solubility in water and ether, water and chloroform, or other immiscible liquids, for the substance in solution distributes itself between the two solvents according to its solubility in each This phenomenon is manifested when anesthetics are administered to obese persons, whose fatty tissue absorbs so much of the anesthetic that it requires a correspondingly larger amount to affect the nervous system It would seem probable, therefore, that a fatty liver would abstract much more chloroform from the blood than a normal liver, and that this chloroform would thus act more strongly and for a longer time on the protoplasm of the fatty liver cells than it would in a normal liver

As to the fact that the necrosis observed in these livers is in the center of the lobules, and that the fatty changes are sometimes central and sometimes peripheral, it would be hazardous to offer an explanation This distribution of the hepatic lesions in the lobule is always a puzzling question, for although we can construct explanations on the basis of the fact that poisons first reach the lobule at its periphery and that the oxygen supply is poorest at the center, yet we always find that exceptions are so abundant for any rule we may attempt to formulate that our attempted explanations of the observed facts have no value For example in phosphorus poisoning in most of the lower animals we find the fatty changes beginning at the periphery of the lobule, yet in monkeys and apes the changes are said to be central, furthermore, another steatogenetic poison hydrazine, always produces the fatty changes in the center of the lobule in the same animals in which phosphorus attacks the periphery

The necrosis of the liver in puerperal eclampsia is ordinarily periph-

eral, and is ascribed to capillary thrombosis Mulzer[7] found that chloroform administered to rabbits rapidly produces fibrinous thrombi in the capillaries, especially of the lungs, but also in the liver and kidneys These thrombi are probably initiated by the clumping of injured red corpuscles, and their development is favored by the increased coagulability of the blood, which develops during the anesthesia It is well known that injection of substances that cause agglutination of the red corpuscles produces extensive necrosis of the liver tissue, but the distribution and appearance of the lesions produced by agglutination thrombi are quite dissimilar to the lesions of chloroform necrosis In my own specimens from two cases, I was unable to demonstrate capillary thrombi by Weigert's fibrin stain, and in other cases in the literature the report of the pathologic anatomy is far too incomplete to permit one to judge as to the presence or absence of such thrombi Of course, it might be possible to explain the anatomic and clinical findings on the basis of capillary thrombosis, if this existed to a sufficient extent, but so far there is no evidence of the occurrence of such a process It has been suggested that chloroform lowers the normal power of the blood to inhibit autolysis, and if this were extensive enough it might account for the sudden autolysis of the liver that appears in chloroform poisoning Studies of the inhibiting power of the serum of animals during chloroform anesthesia might throw some light on this

Two therapeutic hints that have recently appeared seem to be well enough supported by the pathologic and clinical observations to be referred to in closing J H Lyons, of Seattle, in discussing the treatment of puerperal eclampsia,[8] objects to the prevalent custom of suppressing the convulsions by the use of chloroform, often for long periods of time The similarity of the effects of chloroform and puerperal eclampsia on the liver, and the well-established fact that pre-existing injury to the liver predisposes to delayed chloroform necrosis, are certainly weighty reasons for this caution It is also quite probable that chloral is not altogether a safe sedative in cases of this kind, since it is known to produce changes in the liver similar to those caused by chloroform Beddard[9] suggests that in the treatment of chloroform necrosis and more especially for its prevention in cases where it is deemed necessary to use chloroform in spite of possible existing disease of the liver

[7] Mul er Die Amitreten intravitaler Gerinnungen und Thrombosen in der weissen innerer Organe nach Aether und Chloroformnarkosen Munchen med Wchnschr 1907, liv 108

[8] Lyons J H Northwest Med December 1906

[9] Beddard A P A Suggestion for Treatment in Delayed Chloroform Poisoning, Lancet, March 14 1908 p 782

the administration of glucose may be of value   This suggestion is based on Rosenfeld's view that poisoned hepatic cells can utilize carbohydrates well, but proteins and fats only poorly, and that consequently when the cells have used up their meager store of carbohydrate they are unable to utilize the proteins and fats that are available, and hence undergo starvation and death   Experiments have shown that feeding of dextrose to animals lessens the amount of fatty degeneration which results from phosphorus poisoning, and presumably it should have some similar effect in chloroform poisoning

SUMMARY

The cases of delayed chloroform poisoning described in the literature apparently tend to group themselves into two classes   In one, which affects chiefly children, the symptoms are those of "acidemia" or "acetonemia," without jaundice, and in these cases the changes of the liver are not so very marked, consisting, according to the published descriptions, chiefly of fatty degenerations about the periphery of the liver lobules   The other type is observed chiefly in young adults, and clinically is marked by profound jaundice, cholemia, hemorrhages, and the usual symptom-complex of a rapidly fatal acute yellow atrophy of the liver, anatomically the liver appears much as it does in acute yellow atrophy, being reduced in size, flabby, yellow and showing microscopically an extreme degree of necrosis, beginning in the center of the lobule, with more or less peripheral fatty degeneration   Intermediate cases occur that do not fall distinctly into one or the other of the two types   Histologic study of these cases of the second type, to which the name "chloroform necrosis of the liver" may be appropriately applied, shows a striking constancy of structural changes, these consist of total necrosis of all the liver cells, except those at the periphery of the lobule with autolytic disintegration of the necrotic cells and fatty degeneration of those cells that are not necrotic   The capillaries and bile vessels do not seem to be affected, there is no thrombosis and no inflammation or proliferative reaction   Chemical analysis corroborates the histologic evidence of fatty changes and autolysis, there being found a slightly increased amount of fat and the presence of considerable quantities of free amino-acids purins proteoses, peptones and polypeptids derived from the autolysis of the cells

The condition in the second set of cases resembles very closely that of typical acute yellow atrophy of the liver, except in the greater tendency to fatty changes   Nevertheless it seems best for the present to reserve the term acute yellow atrophy to that form of liver necrosis and autolysis

which occurs "idiopathically," and which presents certain features differ-
ent from chloroform necrosis, puerperal eclampsia and phosphorus poi-
soning, and which is possibly due to some specific cause   The fact that
chloroform seems particularly to affect livers in which fatty degeneration
has been previously produced by some other disorder, may possibly be
due to the known absorption of chloroform by intracellular fats, which
in this case would increase the concentration and duration of action of
the chloroform in the degenerated liver cells   Chloroform is a violent
protoplasmic poison and, if it were to inhibit or destroy the oxidizing
enzymes of the liver cells, the results would presumably be quite the
same as those characteristic of chloroform necrosis, hence it seems prob-
able that chloroform produces its effects by acting on the oxidizing
enzymes, without corresponding inhibition of the autolytic enzymes and
the lipase of the cells

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MORPHOLOGY OF THE BLOOD IN PERTUSSIS *

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HISTORICAL

To Frolich[1] of Breslau belongs the credit of having first called attention to the blood in pertussis During an epidemic of this disease in the summer of 1897, he examined the blood in fifty-five cases, making total leucocyte counts in all the cases and differential counts in fifteen In one case he made three counts during three consecutive weeks and in another two counts, in all the other cases the patients were examined but once

Summarizing his results, he says, in conclusion, that in this disease there is a constant leucocytosis and lymphocytosis which in individual cases may show high values The highest counts were noted when the number and severity of the coughing spells reached their maximum, and with the disappearance of these the leucocytosis disappeared He considered, however, that the blood examination would be of no great value because the changes can not be shown early enough in the disease He also said that complications have no material effect on the number of leucocytes In making these examinations he was careful to take the blood at a time of day so as to exclude the physiologic digestive leucocytosis

With the patients making up these fifty-five cases, eight other children were brought to the dispensary by their parents to be treated for whooping-cough, these patients did not have the disease and their blood showed an absence of the characteristic changes

In 1898 Meunier[2] examined the blood in thirty cases of pertussis, making 102 enumerations and ten differential counts He says that the leucocytosis reaches a higher figure than in any other non-febrile affection of children The leucocytosis comes early—in some cases occurring in the catarrhal stage, reaching its height thereafter, diminishing irregularly, and its complete disappearance is not realized until after the end of the whooping period The leucocytosis is more intense among

NORMAL
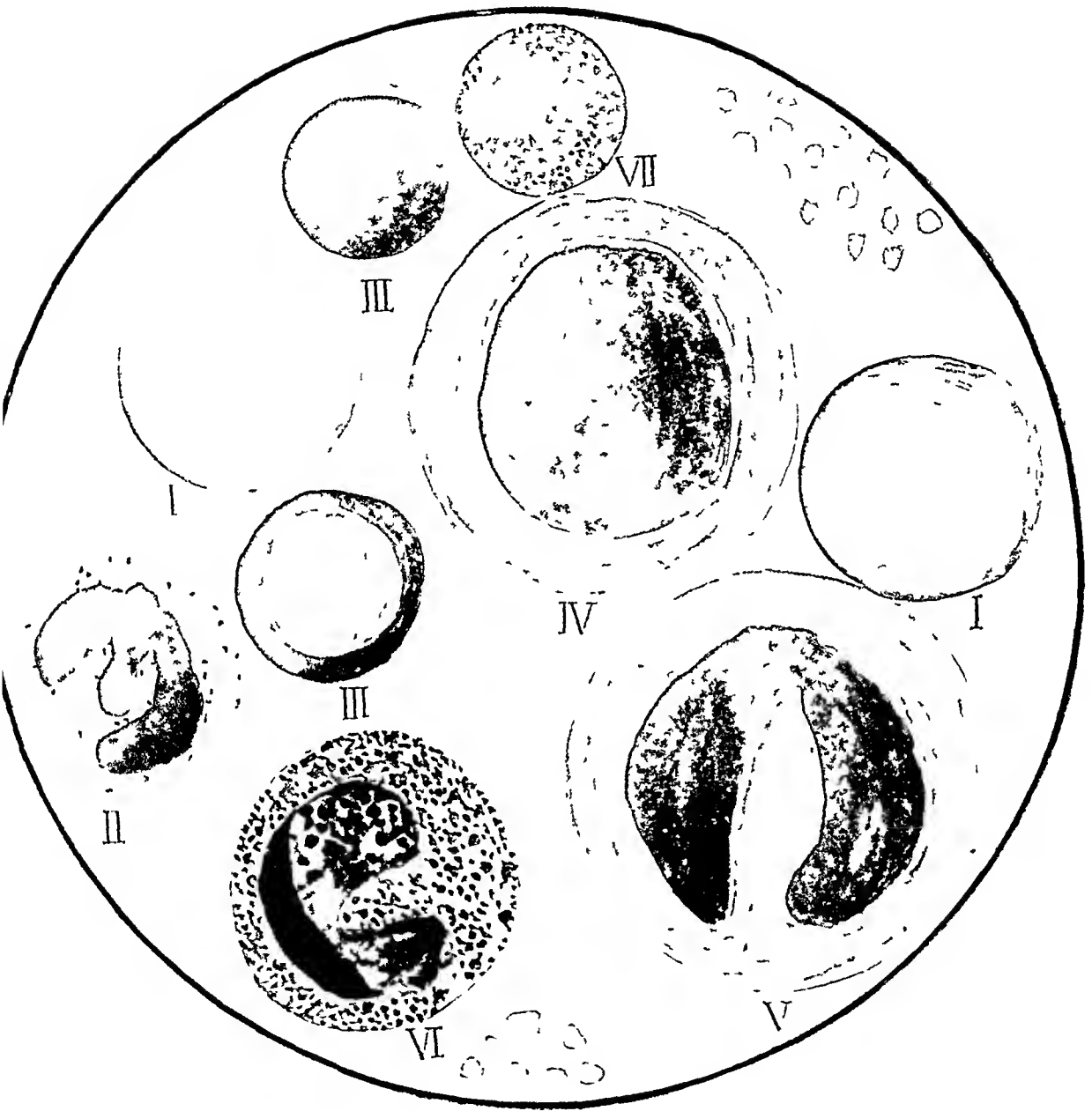
infants of 2 or 3 years and complications have a moderate influence on the count. The increase of the leucocytes, he says, is due to the increase of the lymphocytes, so that the usual blood formula is reversed. During the time of increasing leucocytosis he figures that the polynuclears are doubled, the lymphocytes quadrupled, transitionals tripled and the eosinophiles not affected

De Amici and Pacchioni,[3] in 1899, examined the blood in eighteen cases. On studying their tables I find that, while in three cases they made more than three examinations in each case, yet not in one instance did they examine the same child in the three stages of the disease. They eliminated digestive leucocytosis. To eliminate a possible mechanical element in the causation of this leucocytosis they put some of the children under partial ether anesthesia so that there would be no spasmodic coughing at the time that the blood was taken—and from their results were satisfied that the spasmodic coughing itself had nothing to do with the cause of the leucocytosis

From their studies they conclude that there is in the disease a constant leucocytosis which begins early and continues for a long time after the height of the disease. As a rule, in the first and second stages, there will be found more lymphocytes and in the declining stage a prevalence of polynuclears. They also lay stress on the diagnostic value of the blood examination, because these findings are distinctive and different from those of any of the other respiratory affections with which the disease may be confused

Stengel and White,[4] in 1901, examined three patients with pertussis and found a leucocytosis and lymphocytosis in each of them. Wanstall,[5] in 1903, reports the findings in fifteen cases of pertussis. He made leucocyte counts in but five of these cases and differential counts in all. In examining nineteen children he found that the fifteen patients with pertussis presented more lymphocytes, while the four that proved not to have pertussis showed more polynuclears

Cases have been reported by Cabot[6] and Stevens[7] in which very high leucocyte counts have been found. Muggia and Bertolotti,[8] in 1904, treated twenty-five patients with pertussis with inhalations of ozone from which they claimed highly beneficial results. To prove that this

3 Clin Med Ital, 1899 xxxv 52
4 Univ Penn Med Bull 1902 xiv 318
5 Am Med 1903, v 62
6 'Clinical Examination of the Blood
7 Lancet 1902, ii 791
8 Riv de Clin Ped February 1905

benefit was from the antispasmodic action of the ozone rather than from an antitoxic or antimicrobic action, they set about to examine the blood in a number of these cases. Their findings were. Hyperleucocytosis with predominance of mononuclear cells. These predominating cells they classified as large mononuclears. Their object, however, being the study of the effect from the ozone, they say that "ozone does not change the blood formula, and its action is antispasmodic."

It is interesting to note here that in three severe cases they performed lumbar puncture, and found an increased pressure. When from 15 to 20 c c of fluid was removed there was a marked clinical improvement, and the fluid contained an excess of lymphocytes.

In 1905 Giulee and Phemister[9] examined the blood in fifteen cases, making one leucocyte and differential count each in the paroxysmal stage of fourteen and one in case at the end of the catarrhal stage. They conclude that there is a leucocytosis in all stages of the disease, increasing with the increasing frequency of paroxysms and decreasing when the paroxysms become less frequent and severe. According to their method of classification, they found that in the one case examined in the catarrhal stage the lymphocytosis was due to the small lymphocytes and in the other cases the lymphocytosis was due to the large lymphocytes.

In 1906 Churchill[10] reported on the examination of thirty-six cases, making leucocyte and differential counts in all. Out of sixteen cases in the catarrhal stage, fifteen of the patients showed a lymphocytosis. In complicated cases he found a reversion of the blood formula from the prominence of the lymphocytes to that of the polynuclears. From his own work and a complete study of the literature, which at that time consisted entirely of 100 cases, he says, in concluding, that from the catarrhal stage on there is a leucocytosis and lymphocytosis which distinguishes this disease from others with which it may be confounded.

Considering all of this evidence, we may deduce therefrom that in this disease a leucocytosis due to the lymphocytes begins in the catarrhal stage of the disease, attains its height in the paroxysmal stage and then gradually declines with the subsidence of the clinical symptoms. Complications may or may not alter the whooping-cough formula; the predominating opinion is that this formula is of value in the diagnosis of the earlier stages of the disease.

This evidence still left much to be desired to a better understanding of the interesting blood change. Nearly all of the cases reported by the above investigators were those of patients brought to the outdoor clinics

9 Arch Pediat N Y 1905, xxii 595 599
10 Jour Am Med Assn. 1906, xlvi, 1506

Over these children they had no control and most of them were examined but once The findings in the catarrhal stage of the disease had to be compared with the findings in the paroxysmal stage of others and with the declining stage of still other children The personal equation of each case was lost and the less prominent changes were entirely overlooked

THE AUTHOR'S CASES

During the epidemic of whooping-cough which began in January, 1907 I had the opportunity of studying the blood-picture in this disease and endeavored to carry out the work systematically and more extensively than it had been done before To do this I traced the probable date at which the patients were first exposed the time when they first coughed, when they began to whoop and when the coughing ameliorated

TABLE 1 — CONTROL CASES

Case No	Age	Leuco cytes	Polynu-clears	Lymphocytes Small	Large	Transi-tionals	Eosino-philes
1	1½	10,370	61 0	30 5	4 5	1 0	3 0
2	2	15,280	73 0	23 0	3 5	0 5	0 0
3	2	11 000	82 5	11 5	5 5	0 5	0 0
4	3	12,600	47 5	45 5	5 5	0 0	1 5
5	3	13,300	66 5	26 5	4 5	0 0	2 5
6	3	11,160	53 5	40 5	3 0	0 0	3 0
7	4	10,720	59 5	34 5	4 0	0 5	1 5
8	4	11,300	28 0	55 0	3 0	1 0	13 0
9	4	10 600	37 5	58 0	4 0	0 5	3 0
10	4	7 250	62 0	27 5	5 5	0 0	5 0
11	4	6 800	48 6	45 6	3 6	0 6	1 3
12	4	10 000	54 6	39 1	3 6	0 3	2 6
13	4	17 000	45 1	41 3	1 6	0 3	11 6
14	4	8 600	39 6	52 4	2 8	0 0	5 2
15	4	12 940	32 5	51 3	4 5	1 8	10 0
16	5	11 200	50 0	42 0	5 0	0 0	3 0
17	5	18 300	46 5	45 5	3 5	0 0	4 5
18	5	11 520	51 0	38 0	4 6	0 6	5 6
19	6	9 500	55 0	35 5	3 0	2 5	4 0
20	6	11 000	60 0	29 5	2 5	0 0	8 0
21	6	14,600	60 0	33 5	4 5	0 0	1 5
22	6	7 000	51 25	39 75	7 75	0 25	1 0
23	6	7 200	61 50	32 5	3 0	0 0	3 0
24	6	10 700	63 0	31 5	3 5	0 5	3 0
25	6	9 000	65 6	28 3	1 6	2 0	1 5
26	6	8 120	61 0	31 5	2 5	1 0	1 6
27	7	10 000	69 0	22 5	3 5	0 0	4 0
28	7	9 000	62 5	26 5	7 0	1 0	5 0
29	7	10 400	71 0	23 0	4 0	1 0	1 0
Average		10 567	55 74	35 02	4 06	0 54	3 7

The cases are thus classified and in almost each instance a typical cycle can be seen to have occurred In this way I studied the blood in fifty cases and my findings are uniform enough to assure the value of the blood examination in diagnosis and to establish the blood-picture for the disease

The children in which the disease occurred were of the usual whooping-cough age, the greater part of them being institution children previously healthy   Although such children often come from the lower walks of life and have hereditary taints and predispositions, and being institution children live in hygienic surroundings not so good as those enjoyed by children in private homes, yet the results were in no way different from those in cases which occurred in the families of the members of the Academy, whose children represent the highest grade of child life

These facts assure me beyond doubt that the reaction of the organism to the pertussis infection takes place in a definite way and is associatsd with certain specific manifestations   Of these, the change in the blood formula is one feature

Age
TABLE 2 —AVERAGE AT DIFFERENT AGES						
4	10 578	45 26	44 96	3 7	0 62	6 6
5	10,340	49 0	41 83	4 3	0 2	4 3
6	9,640	59 6	31 28	3 5	0 84	3 0
7	9,800	67 3	24 0	4 8	0 6	1 5

For the sake of brevity I will tabulate in detail only the first thirty cases of this series, not picked cases, but the first thirty that came under my observation   As may be seen (Table 4) the first twenty-nine cases occurred in children from 1½ to 7 years, inclusive, and the thirtieth case occurred in a lady 72 years of age, the mother of a physician   This case I will mention separately   For the normal controls I have made blood counts in healthy children of the same age, living under exactly the same circumstances (Table 1)

As is well known, during the first seven years of life there is a progressive fall in the number of leucocytes, a gradual decrease in the proportion of lymphocytes, and a simultaneous increase of the polynuclears in the circulatory blood   This is distinctly seen in the table of the control cases, excepting in children of the first three years of life   This error, I believe, is entirely due to the small number of cases included   Table 3 gives the average of the control cases at their relative ages

THE TABULATED RESULTS

We might compare the individual cases at their relative ages, but, for the sake of brevity I have arranged each of these tables with sum-totals and averages and the results are distinct and characteristic   The blood was taken always before meal time, so as to eliminate digestive leucocytosis

Table 1 shows the counts in the control cases

Table 2 shows the average counts of the healthy children at their relative ages

Table 3 shows the counts in those cases of the series in which the first blood examination was made within the first week of the coughing at the clinical onset of the disease

TABLE 3 —At Onset

Case No	Age	Leuco-cytes	Polynu-clears	Lymphocytes		Transi-tionals	Eosino-philes
				Small	Large		
1	1½	30 250	65 3	27 6	4 3	2 0	0 3
10	4	11,760	46 0	47 0	5 0	0 0	2 0
11	4	12,000	69 0	18 5	10 0	1 0	1 5
12	4	17 600	54 5	39 0	4 0	0 0	2 5
13	4	28 000	47 5	41 0	4 5	3 0	4 0
15	4	18 100	49 0	41 0	9 0	1 0	0 0
17	4	9,750	35 0	52 0	6 0	3 0	4 0
20	6	15,660	37 3	52 6	5 1	2 0	3 0
22	6	7 300	47 5	45 5	3 0	0 5	3 5
23	6	33 000	71 0	19 0	4 0	0 5	5 0
24	6	10 500	31 5	53 5	7 5	3 0	4 5
25	6	16 000	40 0	52 0	3 0	3 0	2 0
26	6	12 050	43 0	43 0	5 0	0 0	9 0
29	7	23 800	63 0	31 0	4 0	1 0	1 0
Average		17 539	50 06	40 19	5 02	1 42	3 02

TABLE 4 —At Height

Case No	Age	Leuco-cytes	Polynu-clears	Lymphocytes		Transi-tionals	Eosino-philes
				Small	Large		
1	1½	20,400	49 0	42 0	8 0	0 5	0 5
2	2	40 400	27 5	65 5	4 5	0 5	2 0
3	2	32 250	31 5	65 0	1 5	1 5	0 5
4	2	14 880	33 0	48 5	13 5	1 0	4 0
5	2	88 300	27 5	67 5	3 25	0 25	1 5
6	3	21 200	28 0	60 0	5 0	0 5	6 5
7	3	42 720	24 5	69 0	4 0	0 5	2 0
8	4	36 600	34 5	59 5	4 0	1 0	1 0
9	4	13 300	37 0	52 5	8 0	1 0	1 5
10	4	10 220	47 0	39 0	7 0	1 0	6 0
11	4	25 800	50 0	44 5	3 5	0 0	2 0
12	4	10 800	54 0	38 0	5 5	1 0	1 5
13	4	32 250	37 0	59 5	1 5	0 0	2 0
14	4	14 280	35 5	49 0	12 0	0 5	3 0
15	4	26 240	50 0	46 0	2 5	0 0	1 5
16	4	10 500	35 0	49 0	5 0	0 0	11 0
17	5	15 000	47 5	44 0	4 0	1 5	3 0
18	5	11 850	49 0	41 5	7 0	0 5	2 0
19	6	10 800	40 0	47 0	8 0	1 0	4 0
20	6	41 750	41 6	54 6	3 3	0 3	0 3
21	6	16 200	45 5	39 0	7 5	0 5	7 5
22	6	23 500	38 0	47 0	7 0	2 0	6 0
23	6	13 280	27 0	57 0	9 0	0 0	7 0
24	6	49 250	33 0	62 0	3 0	1 0	1 0
25	6	9 400	44 0	41 0	9 0	2 0	4 0
26	6	9 700	30 0	50 0	13 0	2 0	5 0
27	7	13 300	33 5	53 5	4 0	1 0	8 0
28	7	20 000	29 0	60 0	7 0	1 0	3 0
29	7	31 100	49 0	45 0	3 5	1 0	1 5
30	7 2	7 000	32 0	50 0	9 0	1 0	8 0
Average		22 512	38 06	51 52	6 10	0 78	3 56

Table 4 shows the counts at the height of the disease in the spasmodic stage   The highest counts are seen in those patients who my notes show to have been the sickest children

Table 5 shows the counts in those cases in which clinically the patients showed a marked improvement   The average time in which the coughing subsided was two months and eleven days

TABLE 5 — MARKED IMPROVEMENT

Case No	Age	Leuco- cytes	Polynu- clears	Lymphocytes		Transi- tionals	Eosino philes
				Small	Large		
1	1½	5,000	44 0	45 0	6 0	2 0	3 0
2	2	10,500	56 0	27 0	1 0	1 0	15 0
3	2	9,200	45 0	38 0	11 0	3 0	3 0
4	2	12,000	38 0	47 0	4 5	0 5	10 0
5	2	20,200	40 0	52 0	5 5	1 0	1 5
6	3	10,400	44 0	42 5	8 0	1 0	0 0
7	3	6,200	50 0	48 0	1 0	0 0	9 0
8	4	15,500	51 0	34 0	5 5	1 0	2 0
9	4	7,500	42 0	53 0	2 0	2 0	6 0
10	4	6,600	48 0	40 0	4 0	2 5	6 0
11	4	9 400	45 5	44 0	2 0	2 5	3 0
12	4	13,860	60 0	29 5	5 0	1 0	3 5
13	4	11,700	47 0	42 0	6 5	0 0	4 0
14	4	12,200	45 0	47 0	4 0	0 0	4 0
15	4	13,300	48 3	45 0	2 6	0 0	4 0
16	4	7,800	61 0	29 0	6 0	1 0	8 5
17	5	14,200	42 0	42 5	6 0	1 0	4 0
18	5	8,500	50 0	40 0	5 0	0 5	6 5
19	6	10 000	57 5	33 0	2 5	0 0	3 5
20	6	11 750	55 0	35 0	6 0	4 0	5 0
21	6	8 160	49 0	40 0	2 0	2 0	8 0
22	6	11 320	49 0	38 0	3 0	0 0	6 0
23	6	10 200	35 0	49 0	10 0	2 0	9 0
24	6	7 600	37 0	44 0	8 0	2 0	6 0
25	6	8 460	48 0	38 0	6 0	2 0	4 5
26	6	7 800	45 5	42 5	6 5	1 0	7 5
27	7	12 000	48 5	38 0	5 0	1 0	3 0
28	7	9 000	55 0	40 0	2 0	0 0	2 0
29	7	15 428	77 0	18 0	3 0	3 5	8 5
30	72	8 250	57 0	27 5	3 5		5 5
Average		10 451	49 5	39 61	5 1	1 21	5 35

Table 6 shows the counts in the same children after they had been in the country from June to October , at the end of that time they were comparatively in good health

THE BLOOD-COUNT

I will now consider the various elements in the blood-count and the course that they pursued   The control will be Table 1

The Leucocytes as a Whole — Within a week of the first cough there is a marked leucocytosis before the change in the differential formula is really noticeable   The leucocytosis steadily increases reaches its height

m the spasmodic change and then falls by lysis   The average time in which the leucocytes returned to about their normal number was three months and fifteen days after the onset

The Polynucleans—Relatively they seem to fall in number, but absolutely they are increased in a moderate degree

TABLE 6—Eight Months Later

Case No	Age	Leuco-cytes	Poly nu-cleans	Lymphocytes		Transi-tionals	Eosino-philes
				Small	Large		
1	1½	10 560	54 5	36 5	3 5	0 5	5 0
2	2	10 800	41 0	49 5	3 0	0 5	6 0
3	2	13 800	50 5	41 5	4 5	1 0	2 5
4	2	11,600	50 0	36 5	3 5	0 5	9 5
5	2						
6	3	9 500	57 5	29 0	3 5	3 0	7 0
7	3						
8	4	8,600	57 0	36 0	2 0	1 0	4 0
9	4	6,800	56 0	40 0	3 0	1 0	0 0
10	4	8 800	66 0	25 0	5 0	2 0	2 0
11	4	14 300	57 0	35 0	1 5	0 5	6 0
12	4	12,200	50 0	40 0	2 0	1 0	7 0
13	4	7 800	56 0	35 0	0 0	1 0	8 0
14	4	10 500	69 0	25 0	4 5	1 0	0 0
15	4	20 750	55 5	40 5	2 5	0 0	1 5
16	4	9,060	68 0	24 0	5 0	2 0	1 0
17	5	6 200	47 5	39 5	4 5	0 0	8 5
18	5	10 900	71 0	21 0	5 0	2 0	1 0
19	6	9 300	49 5	37 0	3 0	1 0	9 5
20	6	8 500	47 0	41 0	3 5	0 5	8 0
21	6	9 200	70 0	20 0	5 0	1 0	4 0
22	6	14 300	61 0	21 0	6 0	1 0	11 0
23	6	9 800	63 0	18 0	4 0	4 0	11 0
24	6	11 600	69 0	24 0	2 0	1 0	4 0
25	6	10 600	72 0	19 0	7 0	0 0	2 0
26	6						
27	7						
28	7	1 300	59 0	27 0	5 0	0 0	9 0
29	7	12 100	62 0	32 0	5 0	0 0	1 0
30	72						
Average		10 355	58 0	32 0	4 0	1 0	5 0

The Small Lymphocytes—These are the most prominent elements in the blood change   Their increase begins early in the disease at times I believe before the child coughs   From that time on they continue increasing in number and reach their height in the spasmodic stage   Then fall is gradual by lysis and they reach their normal numbers in about three and a half months

The Large Lymphocytes—These follow nearly the same course as do the small variety   They increase from the onset reach their height in the spasmodic stage and decrease thereafter   I did not find that their number was highest in the cases that had the highest grade of small cell

lymphocytosis, not *vice versa*. In one case a count showed 18 per cent.
This was the highest. Nothing else could be associated with it either in
the blood-picture or clinically. On carefully studying these cells I find
that their numbers are highest at a period which does not exactly coin-
cide with that at which the small lymphocytes are most numerous; it
appears to be slightly later. This might mean that these cells represent
the final reaction of the lymphocytes or perhaps of the tissues from
which these cells are derived, to the pertussis infection. While it is Table
4 that shows their highest numbers, yet that is not the time when they
reached their greatest height. These tables show only four of the aver-
age number of eight counts that were made in each case.

The Transitionals.—The course of these cells seemed very irregular.
They were distinctly less numerous during the height of the lympho-
cytosis, and comparison with each of the other elements at the different
stages of the disease reveals nothing.

The Eosinophiles.—The rôle played by the eosinophiles is distinctive.
At the beginning and during the lymphocytosis they are present in
about their normal proportions. Somewhere near the third month of the
disease, at about the time of recovery, an eosinophilia begins and may
continue for several months. In Table 5, which represents the time of
marked improvement, out of the thirty cases, twenty of the patients had
an eosinophilia averaging 6.75 per cent. Of the remaining ten cases
seven of the patients showed an average count of 8.16 per cent on the
examination immediately before or after the time of the examination in
the other cases. This leaves but three cases out of the thirty that at the
time of recovery did not present an eosinophile count distinctly above the
normal.

On studying the control table (Table 1) we find that the apparently
healthy children present a variation of from 1 to 13 per cent of eosino-
philes. Yet the regularity with which the increase of eosinophiles above
their normal average proportion occurs in the disease at the time of re-
covery leads me to believe that the eosinophile has a part of its own in
this blood cycle.

These are the more commonly recognized elements of the differential
blood count; but in these examinations I have often seen other cells that
are worthy of mention.

Mast Cells.—These were conspicuously noted in thirty-eight out of
fifty cases and they never exceeded 1 per cent. Their relationship was
as follows:

To the total leucocyte count they bore no relation.

To the polynucleais and small mononucleais   Out of thnty-eight cases, at the time when the mast cells weie noted twenty-thiee showed a gieatei numbei of polynucleais, the othei fifteen cases showed moie small lymphocytes

To the laige lymphocytes   Theii piesence was noted moie fie-quently about the time the laige lymphocytes weie high

To the tiansitionals   No ielation

To the eosinophiles   No distinct ielation, but they occuiied moie often when the eosinophiles weie above the noimal

On the whole, we find that they weie moie fiequent about the time of iecoveiy

Bilobate Small Lymphocytes —These cells weie veiy often piesent, duimg the stages of active lymphocytosis, which means duimg the fiist thiee oi foui weeks of the infection

Degeneiated Laige Lymphocytes —The laige "basket foims' and smallei foims weie also fiequently seen duimg the active lymphocytosis

Myelocytes with eosin and basophile gianules weie occasionally noted

Basophile cells, containing both basophilic and eosinophilic gianules, weie also noted seveial times

Blood plates weie seen in veiy laige numbeis in two cases after ciises fiom pneumonia complicating the disease   This is the so-called *ciise hemotoblastique* of Hayem, who says that the occuiience of laige num-beis of plates comes with the iecoveiy fiom the disease (pneumonia) In none ot the othei cases weie they seen in laige numbeis, although they weie always piesent

THE ADULT CASE

The adult case which occuiied in a lady 72 yeais of age was clinically unmistakable   She had the disease at the same time that hei thiee giandchildien weie having it   The fiist count was made duimg the spasmodic stage and the following ones accoiding to given dates   Theie was no leucocytosis in this case but the foimula was distinctly ieveised See Table 8

COMPLICATIONS

Complications have theii effect on the blood foimula in a veiy chai-acteiistic way   As will be seen (Table 7) the iespiaioiy oigans weie most commonly involved and the complications weie as follows   Two cases of bronchopneumonia two cases of pleuiopneumonia and one case of suppuiative otitis media

Table 7 shows the effect on the blood foimula in each instance   In the pneumonias the leucocytosis was inciaised and the polynucleais be-

came at once the prominent cells As soon as the pneumonias subsided, the leucocytes fell and the lymphocytes became prominent, a reversion to the pertussis formula De Amici and Pacchioni,[3] Cabot[6] and Churchill[10] report cases complicated by pneumonia, and their findings seem at variance

TABLE 7 —Complications

Date	Leuco cytes	Polynu clears	Lymphocytes Small	Lymphocytes Large	Transi tionals	Eosino philes
CASE 1 BRONCHOPNEUMONIA						
Feb 9, 1907	49,280	33 0	62 0	3 0	1 0	1 0
Feb 14, 1907	64,000	49 0	41 5	8 0	0 5	1 0
Feb 25, 1907	32,000	39 3	54 3	6 0	0 0	0 3
March 10, 1907	13,800	60 0	31 0	5 5	1 0	2 5
CASE 2 BRONCHOPNEUMONIA						
Feb 5, 1907	7,300	47 5	45 5	3 0	0 5	3 5
Feb 20, 1907	18 250	66 0	21 0	5 0	2 6	4 0
Feb 28, 1907	16 200	45 5	39 0	7 5	0 5	7 5
CASE 3 PLEUROPNEUMONIA DIED						
Jan 26, 1907	39 000	37 0	56 0	4 5	1 0	1 5
Feb 2 1907	62,750	53 0	34 5	9 0	1 5	1 5
Feb 18, 1907	74,000	70 8	22 0	5 5	0 8	0 16
CASE 4 PLEUROPNEUMONIA						
Jan 18, 1907	38,800	28 7	65 4	4 53	0 58	0 8
Jan 24, 1907	53,000	60 3	36 6	2 6	0 3	0 0
Feb 3, 1907	19,800	30 0	57 5	11 0	1 5	0 0
CASE 5 SUPPURATIVE OTITIS MEDIA						
Jan 26, 1907	30,250	65 3	27 6	4 3	2 0	0 3
Jan 31, 1907	19,830	47 5	41 5	7 5	2 5	1 0
Feb 26, 1907	10,250	32 0	42 0	18 0	3 0	5 0

TABLE 8 —Adult Cases

Date	Leuco cytes	Polynu clears	Lymphocytes Small	Lymphocytes Large	Transi tionals	Eosino philes
March 4, 1907	7,000	32 0	50 0	9 0	1 0	8 0
March 12, 1907	7 700	53 0	38 5	5 0	0 5	3 0
April 18, 1907	8,250	57 0	27 5	3 5	3 5	8 5

A number of the patients in these fifty cases during the paroxysmal stage were sick enough to be put to bed At these times I examined their chests when I took the blood specimens and from those observations my belief is that so long as there exists but a severe bronchitis with perhaps small areas of consolidation the lymphocyte formula will be retained but just as soon as a distinct consolidation is present the formula will be reversed and the polynuclears will predominate

In the case of suppurative otitis media the complication was present when the first count was made at the onset of the whooping-cough after

the ear was drained, the leucocyte count at once fell and the cells assumed the characteristic formula

In five cases the patients gave a history of having had the disease before They were patients in Cases 10, 22, 23 and 30 Of these, the patient in Case 10 did not show a lymphocytosis, the others were typical

SUMMARY

After a careful study of these cases individually and in the aggregate in which on an average eight leucocyte and differential counts were made in each case, at regular intervals, the blood cycle in this disease appears to occur as follows

There is at first a leucocytosis with increase of all the forms, then a small cell lymphocytosis becomes conspicuous and continues to increase when the other forms have reached their limit The large lymphocytes follow the course of the small ones, but they reach their greatest numbers after the small cells have reached theirs During the stage of active lymphocytosis, bilobed small lymphocytes are frequently seen as well as numerous degenerated large lymphocytes, especially the basket forms

Then comes the simultaneous falling of the leucocytosis and lymphocytosis, while the polynuclears begin to resume their normal proportion A little later the mast cells are observed more frequently, and an occasional myelocyte may be seen While the leucocytosis and lymphocytosis continue to fall by lysis, an eosinophilia is noted this continues for a variable time after which the blood formula resumes its normal proportions During this entire cycle the transitionals seem unaffected

If we were to speak of the first and second half of the blood cycle in this disease we would say that in the first half the lymphocytes are the prominent factors and in the second half the polynuclears and the eosinophiles

Clinically leucocytosis is present at about the time the child first coughs as the coughing goes on the leucocytosis increases and the lymphocytosis becomes very marked A glance at the tables gives an idea of the numbers The height of the leucocytosis is reached in the spasmodic stage sometimes early and sometimes in the latter part the sickest children showing the highest grade of leucocytosis About the time that a marked improvement is noted in the child the leucocytosis has declined the polynuclears have increased and the eosinophilia is present The eosinophilia continues for a variable time

Little more need be said of the distinct value of blood examination in early diagnosis of the disease Within the last two months I have

been able to make correctly for other physicians three negative and two positive diagnoses before clinical signs were decisive

I wish to express my thanks to Dr Ewing W Day, Dr T J Eltenich, Dr P J Eaton and Dr Lawrence Litchfield for the clinical material that they have placed at my disposal in carrying on this investigation, and to Dr E G Matson and Dr G Conti for their kind assistance in translating the original articles from which I have quoted in the first part of this paper

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EXPERIMENTS WITH AN ASH-FREE DIET

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The introduction of standard test diets into clinical medicine has distinctly advanced our knowledge of human metabolism and furnished many useful data for diagnosis, prognosis and treatment   Such are the Ewald test breakfast, the diet of Schmidt and Strassburger for the study of diseases of the gastrointestinal tract and the proteid-fat diet employed in diabetes   Although these various diets were excellent, they threw light on only the more superficial phenomena of metabolism, and it was to be expected that other variations in the diet would be planned which would penetrate into the more fundamental processes of the body   It is to the credit of Taylor[1] that he devised such a diet in 1904 and had the temerity to live on it until unusual symptoms occurred

Admirable as was the conception and interesting as were the results of Taylor's experiments with an ash-free diet, one of his observations and the interpretation he later placed on it were so at variance with prevailing ideas as to attract our attention   He writes   ' On the ninth day a colleague noted·in the breath a strong odor of acetone   Investigation thereon revealed in the urine notable quantities of acetone and diacetic acid without β-oxybutyric acid "   At the session of the Association of American Physicians held in 1907 this observation was cited by Taylor as an argument against the generally accepted theory of acidosis of the β-oxybutyric type, which ascribes its occurrence to the lack of oxidation of carbohydrates in the metabolism   His criticism apparently was fully justified, because, according to his experiment, an acidosis developed in a healthy individual on a diet which maintained equilibrium and contained 200 grams of carbohydrates which were known to be assimilated

The overthrow of any theory which has served so many useful purposes as the secondary oxidation theory proposed by Nasse and adopted by Naunyn can hardly be considered accomplished by a single experiment   It, therefore, seemed well worth while to repeat the work, particularly because, so far as we are aware, no further evidence has been offered which would confirm it   The mere detection of acetone in the breath by

1 Taylor   Studies on an Ash-free Diet, Univ of Calif Pub , Pathology, 1904, 1, p 71

the sense of smell can not be accepted as a sufficient guarantee of its presence Indeed, Folin's recent observations[2] make it probable that the so-called "acetone breath" has nothing to do with acetone The actual quantity of acetone in the urine is not given by Taylor, but at the most the acidosis must have been slight, because the ammonia-nitrogen nitrogen ratio reached but 9 5 per cent Convincing proof that acidosis of the acetone type was due to the withdrawal of salt might have been afforded if an acidosis thus produced had disappeared on the addition of salt to the diet without other change in the plan of the experiment

Our experiments followed exactly the methods suggested by Dr Taylor Two healthy medical students, Mr Sawyer and Mr Smith, consented to act as subjects [3]

The daily diet consisted of the whites of 18 eggs, 120 gm olive oil, and 200 gm of crystallized sugar The albumin was prepared in the following manner Eighteen hundred c c distilled water (100 c c to the white of each egg) were heated in a double boiler up to 56 degrees C The whites of the eggs, previously broken up with a glass rod until homogenous, were then poured in, and at first stirred briskly, but later more slowly until the temperature reached 100 degrees C Twelve c c of acetic acid, diluted by one-fifth, were added and the clear fluid decanted off from the precipitated albumin The precipitate was thoroughly mixed with 1,000 c c distilled water, heated nearly to the boiling point and again decanted, this procedure being repeated three times The albumin was then transferred to a large Buchner filter and again washed three or four times with hot distilled water The final filtrate was nearly free from chlorin The sugar was given in the form of rock candy, of which the ash was non-weighable The olive oil was washed half a dozen times in a large separating funnel with distilled water Distilled water alone was drunk and in measured quantities

Bone-black was used in the demarcation of the stools and was taken with the last regular meal, which was twelve hours before the commencement of the experiment, and again on its completion just before a return to an ordinary diet

The first experiment was begun Nov 29, 1907, and continued for thirteen days Mr Sawyer s observations during this period are given in his own words He writes

2 Folin, Otto Chemical Problems in Hospital Practice, Jour Am Med Ass'n 1908 1 p 1391

3 Mr Sawyer and Mr Smith lived at the New England Deaconess Hospital during the course of the experiment, and to that institution we are much in debted for the many courtesies we received

The albumin was the most disagreeable part of the diet I used a syrup with this so as to give it a taste and in this way it was more easily swallowed, but to the end this proved to be the most irksome part of the experiment During the time of the dieting I worked between seven and eight hours at the school, at least half of which time I was standing I spent about two hours of each of the two Sundays that intervened in walking I slept longer than I usually do, averaging about nine and one half hours in the day There were two nights, however, during which I lost about three hours on account of indigestion With the loss in weight there was also loss in strength, and I found myself more easily winded and more easily tired On some of the evenings of the more strenuous days I was quite exhausted On two occasions I had a slight fainting attack Three evenings before the termination of the experiment I had some symptoms of indigestion, namely, the distress from abdominal distension, hiccough and some belching of gas My appetite throughout was good, at times ravenous, but not for the ash-free diet to which I never looked forward What discomfort there was to the experiment did not progress from first to last Some of the days earlier in the experiment were more trying than the last

The diaphoresis which Dr Taylor observed throughout was noted neither by Mr Sawyer nor observed by us Mr Sawyer s symptoms were not progressive in character, and in this respect he differed both from Dr Taylor and Mr Smith The daily quantity of chlorin in the urine steadily decreased, and on the tenth day reached 0 22 gm, but as the breath and urine gave no evidence of the presence of acetone or diacetic acid the experiment was continued On the eleventh day the chlorin remained the same, but on the twelfth day it fell to 0 17 gm, or 0 02 gm less than the lowest limit reached by Taylor Tests for acetone and diacetic acid still being negative, the diet was continued for another twenty-four hours The chlorin on this, the thirteenth, day was the same as on the twelfth but acetone and diacetic acid still failed to appear, and the experiment was, therefore, discontinued On two subsequent days, namely the second and fourth, the urine was again collected

The reaction of the urine was acid throughout, and daily tests failed to reveal the presence of albumin, sugar or, as already recorded, acetone or diacetic acid Le Nobel's test was used for the determination of acetone, and Gerhardt's ferric chlorid test for the diacetic acid With few exceptions these were performed in the presence of Dr Folin The color of the urine was uniformly normal for the first nine days, but became slightly high on the tenth and eleventh and distinctly high on the twelfth and thirteenth Indican was present in variable quantities as shown qualitatively, gradually decreasing from the first to the sixth day, and then gradually increasing up to the end of the experiment The urinary sediment gave no evidence of disease of the kidneys Tables 1, 2 and 3 give the analytical details The nitrogen was estimated by

the Kjeldahl method, and the ammonia creatinin, sulphates and total sulphur by the Folin method [4]

The weight of the dried feces was 121 68 gm, or about 9 0 gm per day   This is two or three times the weight of the feces of a starving individual   The total quantity of fat in the feces amounted to 53 2 gm, and as the total fat in the diet was 1,560 gm   the total quantity of fat absorbed was 96 6 per cent   The total nitrogen in the feces was 6 05 gm If the total nitrogen in the diet for the thirteen days is estimated at (11 5 x 13 =) 150 gm, the percentage of nitrogenous food absorbed was 96

The excellent absorption of the protein and fat is striking and deserves emphasis   It is a most useful point to bear in mind in the treatment of patients   So much has been attributed to the psychic phenomena of digestion that it is well occasionally to have proof that an uninviting and positively distasteful diet, which does not awaken the least suspicion of an appetite, may be thoroughly assimilated

It is evident from the table that Mr Sawyer was in nitrogenous equilibrium, because the total nitrogen for the thirteen days was nearly constant, varying from a maximum of 10 7 gr to a minimum of 12 18 gr, the daily average being 11 5 gm

The chlorin is the center of interest because this inorganic salt comprises such a large percentage of the inorganic salts in the urine, and further because of the importance which recent work has assigned to it in metabolism   Its gradual diminution during the thirteen days is mathematical proof of the accuracy of the experiment   The amount of chlorin excreted, 12 94 gm, corresponds to the figures which were obtained in the experiments on Cetti and Breithaupt and those of Belli and Wundt   In the first two days more salt was excreted than in the remaining eleven days, a striking proof of the tenacity with which the body retains its chlorin   For the last five of the thirteen days of the experiment the excretion was practically constant at 0 2 gm   The data show well the limitations of the withdrawal of salt   and again furnish proof that only about 15 per cent of the total chlorin in the body can be removed   On the conclusion of the experiment Mr Sawyer returned to his ordinary diet eating however with moderation   Two days later the total quantity of chlorin excreted was only 3 5 gm   despite the fact that he had used rather more salt than was customary   but after four days of the ordinary diet the chlorin amounted to 25 76 gr   and the quantity of urine reached a total of 1,090 cc   For this great increase

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4 Folin   Jour Biol Chem 1906, 1, 131

in the excretion of salt and water we have no explanation, and speculation is unprofitable because of the unknown character of the ingesta In the next experiment we attempted to follow this point more closely

The weight can be brought into connection with the chlorin because the two varied together Sawyer lost 2 8 kg during the first three days of the experiment, but in the remaining ten days only 2 5 kg Taylor reports a loss of 1 5 kg "during the period" Probably this statement refers to the change in weight from his third to ninth day Quite as striking as the loss of weight during the experiment was the gain of 4 1 kg in the first seventy-two hours following its completion Whereas the addition of salt to the diet of a healthy person has little effect due to its ready elimination, the withdrawal of salt from the diet is of more significance, because along with it goes a lowering of body weight by removal of water This fact must always be borne in mind in any experiment in which weight is a factor

The loss of 10 per cent of body water is said to produce a moribund condition in thirsting animals, but the conditions of our experiment were different in that the loss of water was coincident with the loss of salt, and so in a way physiologic

The intake of water was nearly constant, diminishing slightly as the experiment progressed The possibility that this diminution in the supply of fluid was concerned in the loss of weight was excluded in the second experiment by keeping the intake of water at a constant level of 2,000 c c Less fluid was voided than water drunk, corresponding to the well-known fact that a considerable percentage of the water excreted passes out by the lungs and skin Thirst was not a symptom in the experiment, and, indeed, would appear to vary with different individuals Thus Taylor (weight 80 kg) desired over two liters of water daily, Sawyer (weight 70 kg) was comfortable with 1,300 c c, and Smith (weight 55 kg) found only a little less than two liters sufficient No constant relation can be drawn between the intake of water and the excretion of urine in this experiment

A steady diminution in the excretion of phosphoric acid took place, but this was not as marked as was the decrease in chlorin Our values for phosphoric acid are calculated as P_2O_5, while Taylor's are estimated in terms of PO_4 The actual quantity of phosphorus excreted, therefore, was a trifle lower in Sawyer's case than in Taylor's experiment

The quantity of ammonia was fairly constant from beginning to end, varying from 0 94 gm on the first day to 1 26 gm on the tenth The ammonia-nitrogen nitrogen ratio was nearly uniform throughout In percentage as well as in absolute quantity it was, however, slightly higher

than the results recorded by Folin [5] This is readily accounted for by the fact that in our experiment the alkalin salts of the egg whites have been removed

The creatinin was the most constant factor of all, the lowest quantity being 1 47 gm and the greatest 1 6 gm   The percentage of creatinin-nitrogen to the total nitrogen varied from 4 6 to 5 4   This percentage is greater than Folin found to be the case with his normal diets, but less than that of healthy individuals on his cream-starch diet   This variation in percentage is accounted for by the total protein of the ash-free diet being considerably lower than that of the standard diet and greater than that of the cream-starch diet   The total quantity of creatinin, however, was practically the same, thus Folin found the average for thirty normal urines to be 1 55 gm creatinin, and the average in Sawyer's case was 1 54 gm   This is identical with the calculated value for creatinin for an individual of Sawyer's weight, namely 1 54 gm (22 mg creatinin per 70 kg body weight), a further illustration of its dependence on body protein rather than on the protein of the food

TABLE 1—INTAKE OF WATER, URINARY ANALYSIS, WEIGHT

Day	H₂O c c	Urine c c	Sp Gr	P₂O₅ gm	Cl gm	Weight kg
1	1470	1720	1012	1 29	4 60	70 2
2	1550	1810	1010	1 29	2 52	
3	1560	1430	1012	1 28	1 88	
4	1290	930	1017	1 20	0 87	67 4
5	1290	1100	1013	1 43	0 69	
6	1545	1170	1012	1 04	0 48	66 6
7	1200	850	1015	1 15	0 46	
8	1125	1000	1013	0 78	0 40	66 1
9	1290	1160	1011	0 95	0 26	
10	1200	860	1015	0 89	0 22	
11	1260	650	1018	0 76	0 22	
12	1215	510	1023	0 79	0 17	65 1
13	1170	560	1023	0 86	0 17	64 9
14						
15		940	1029		3 50	
16						69 0
17		4090	1017		25 76	

The uric acid nitrogen was also practically constant but the percentage was considerably lower than found by Folin in his normal urines This is in conformity with his idea that the actual amount of uric acid diminishes along with the diminution of the total nitrogen even apart from the purin nitrogen of the food

5 Folin Otto Approximately Complete Analyses of Thirty "Normal' Urines, Am Jour Physiol 1905 xiii 45 Laws Governing the Chemical Composition of Urine Am Jour Physiol 1905, xiii 66

The urea represents the chief variable in nitrogenous metabolism It was low in this experiment, due undoubtedly to the constancy of the excretion of creatinin and the diminution in total nitrogen Our values for the undetermined nitrogen correspond to those usually found

TABLE 2 —NITROGEN METABOLISM IN EXPERIMENT ON SAWYER

Day	Total—N₂ gm	Urea—N gm	Ammonia—N gm	Creatinin—N gm	Uric Acid—N gm	Undetermined—N gm	Urea—N P C	Ammonia—N P C	Creatinin—N P C	Uric Acid—N P C	Undetermined—N P C
		20 7	*0 94*	*1 60*	*0 18*						
1	11 49	9 66	0 78	0 58	0 06	0 41	84 1	6 8	5 0	0 5	3 6
		18	*1 02*	*1 47*	*0 16*						
2	10 27	8 39	0 85	0 55	0 55	0 43	81 7	8 3	5 4	0 5	4 1
		20 6	*1 04*	*1 58*	*0 20*						
3	11 67	9 62	0 87	0 59	0 06	0 53	82 5	7 5	5 0	0 5	4 5
		18 8	*1 12*	*1 51*	*0 22*						
4	10 73	8 75	0 93	0 56	0 07	0 42	81 5	8 7	5 2	0 7	3 9
		18 9	*1 13*	*1 56*	*0 22*						
5	10 86	8 81	0 94	0 58	0 07	0 46	81 1	8 7	5 4	0 6	4 3
		19 1	*1 17*	*1 53*	*0 21*						
6	10 91	8 74	0 97	0 57	0 07	0 56	80 1	8 9	5 3	0 7	5 0
		19 4	*1 15*	*1 54*	*0 19*						
7	10 72	8 84	0 96	0 57	0 06	0 29	82 5	9 0	5 3	0 6	2 7
		22 7	*1 24*	*1 50*	*0 21*						
8	12 18	10 02	1 03	0 56	0 07	0 50	82 0	8 5	4 6	0 6	4 3
		21 2	*1 24*	*1 59*	*0 22*						
9	11 86	9 65	1 03	0 59	0 07	0 52	81 4	8 7	5 0	0 5	4 4
		20 7	*1 26*	*1 51*	*0 20*						
10	11 54	9 23	1 05	0 56	0 06	0 64	80 0	9 1	4 8	0 5	5 6
		17 9	*1 15*	*1 55*	*0 19*						
11	10 07	8 16	0 96	0 58	0 06	0 31	81 0	9 6	5 8	0 6	3 0
		18 8	*1 24*	*1 51*	*0 16*						
12	10 99	8 77	1 03	0 56	0 05	0 58	79 8	9 3	5 0	0 5	5 4
		20 9	*1 21*	*1 51*	*0 16*						
13	11 60	9 37	1 01	0 56	0 05	0 70	80 4	8 6	4 8	0 4	5 8

The total sulphur in the urine was only about one-third that excreted by individuals living on the standard normal diet This must be borne in mind in the interpretation of the results obtained for inorganic and ethereal sulphates and neutral sulphur The ethereal sulphates diminished in the same proportion as the total sulphur with the result that the percentage of ethereal sulphates remains the same as that obtained for the healthy man on the standard normal diet The actual quantity of neutral sulphur, however, did not decrease but stayed practically unchanged As a result the percentage of neutral sulphur in the urine rose from the usual average of 5 to an average of 15 3 Neutral sulphur thus behaves in a similar manner to creatinin Our results approximate those obtained by Folin in his experiments with the low pro-

tem or starch and cream diet   The inorganic sulphates are here the variable which offsets the increased percentage of neutral sulphur

Our first experiment thus failed to confirm Taylor's observation on the influence of a salt-free diet on the production of acetone   The question thus stood simply one experiment against another and it seemed wise to perform a third under slightly different conditions to eliminate the personal equation   The subject, Mr Smith, weighed much less than either Dr Taylor or Mr Sawyer, namely, 55 kg   The experiment was begun on February 15 and ended February 26, but for four days previous to it Mr Smith lived on a diet poor in salt   By means of this preliminary and partially salt-free period several days were saved and we were enabled to study the effect of the addition of salt in the latter part of the experiment without too great prolongation of the same   The plan was successful, for on the first day the chlorin in the urine was found to have fallen to 1 43 gm   The details of the experiment were the same as above reported   Mr Smith found the diet quite as unpalatable as did Mr Sawyer   On the second day he records in his notes   "Felt well except for slight nausea after meals"   The nausea persisted, but on the fifth day was less and did not return until the ninth day   Flatulency was noted on the third day with cramp-like pains and heaviness in the epigastrium, and on several of the days the stool was loose   Some loss of energy was manifest on this and the subsequent days, but it had disappeared by the seventh, when the record states, "No nausea, felt well,' and on the eighth, "No nausea, appetite good '   The ninth day of the experiment was a trying twenty-four hours "considerable nausea all day, had great difficulty in eating my meals on account of the nausea and sense of fulness   Felt weak and in low spirits, some abdominal distress," but the symptoms improved the following morning (tenth day) , ' passed a good night and felt much better, nausea, however, was marked all through the forenoon '   Twelve gm salt were now added to the daily diet and the following change in the record is interesting   "At lunch took salt for first time with great relish   All nausea and epigastric distress disappeared after lunch . in evening felt very decided increase in strength and energy   Eleventh day   "No nausea or distress of any kind great improvement in tone, physical and mental '   It is only fair to state that Mr Smith was aware that within three days from the commencement of his taking salt the experiment would definitely end, whereas up to this point the duration of the experiment was indefinite   He himself felt that "hope long deferred maketh the heart sick ' and was not positive that the improvement in his feelings was wholly due to the salt

The urine was examined for the first ten days daily for albumin, sugar, acetone and diacetic acid, but all of these substances were absent The color remained normal throughout The examination of the urinary sediment revealed no abnormal elements Table 4 contains the result of the analyses

Considerable difficulty was experienced in drying the feces They were, therefore, first extracted with petroleum ether, and this extract made up to 1,000 c c The fat and nitrogen were then determined in each separately and the results combined Before extraction the weight of the feces was 113 gm , after gross extraction, 51 62 gm dried to constant weight The total quantity of fat extracted from the feces was 80 30 gm , and, as the amount of fat ingested during the nine days was

TABLE 3 —SULPHUR METABOLISM IN EXPERIMENT ON SAWYER

Day	Total Sulphur	Inorganic Sulphates	Ethereal Sulphates	Total Sulphates	Neutral Sulphur	Inorganic Sulphates	Ethereal Sulphates	Total Sulphates	Neutral Sulphur
	gm	gm	gm	gm	gm	P C	P C	P C	P C
1	0 96	0 71	0 05	0 76	0 20	74 0	5 2	79 2	20 8
2	0 97	0 76	0 06	0 82	0 15	78 3	6 2	84 5	15 5
3	0 99	0 79	0 06	0 85	0 14	79 8	6 1	85 9	14 1
4	0 98	0 82	0 06	0 88	0 10	83 6	6 1	89 7	10 3
5	1 04	0 81	0 08	0 89	0 15	77 9	7 7	85 6	14 4
6	1 09	0 86	0 07	0 93	0 16	78 9	6 4	85 3	14 7
7	1 06	0 83	0 07	0 90	0 16	78 3	6 6	84 9	15 1
8	1 17	0 90	0 10	1 00	0 17	76 9	8 6	85 5	15 5
9	1 15	0 90	0 05	0 95	0 20	78 3	4 3	82 6	17 4
10	1 12	0 88	0 08	0 96	0 16	78 6	7 1	85 7	14 3
11	1 01	0 80	0 05	0 85	0 16	79 2	5 0	84 2	15 8
12	1 08	0 85	0 07	0 92	0 16	78 7	6 5	85 2	14 8
13	1 10	0 86	0 07	0 93	0 17	78 2	6 3	84 5	15 5

1 080 gm the quantity of fat absorbed was 92 per cent The nitrogen in the dried feces amounted to 2 992 gm If the nitrogen in the diet is reckoned as 103 5 gm , the absorption of nitrogen was 97 per cent

It was intended to allow but 1,500 c c of water daily, but thirst became so troublesome that this quantity was increased on the first day and permanently changed to 2,000 c c from the fifth day on It is interesting to note that the quantity of urine was only slightly greater than in the experiment with Sawyer or in Taylor's experiment The average daily quantity of urine in Taylor's experiment was 1,172 c c , in Sawyer's 1,240 c c , and in Smith's 1,445 c c

The chlorin was but 1 43 gm on the first day, due, as has been said, to the partial salt-free diet for the previous four days It then decreased with slight variations until on the ninth day the total quantity of chlorin

was 0 17 gm , the limit reached in the experiment with Sawyer, and 0 2 gm lower than that attained by Taylor   No sign of acetone or diacetic acid appearing, 12 gm of salt (7 11 gm chlorin) were added to the diet It will be seen that nearly the whole of this quantity was retained in the body, for on the following day only 1 6 gm were eliminated, and even on the next day only 2 26 gm chlorin, but during the third day of the administration of salt the chlorin excreted showed a decided increase, and presumably an equilibrium was soon obtained   Neither on these three nor during the following days was a polyuria, as in Sawyer's case, observed   Thirty-one per cent, or 12 83 gm chlorin, was retained in these three days

TABLE 4 —Intake of Water, Weight, Urinary Analysis in Experiment on Smith

Day	H²O c c	Urine c c	Total N² gm	NH³ gm	Ammonia—N P C	P²O⁵ gm	Sp Gr	Cl gm	Weight kg
1	1820	1810	10 9	58	4 4	2 08	1009	1 43	*55 5
									54 8
2	1500	1400	11 1	61	4 5	1 09	1009	1 11	54 3
3	1500	1190	9 8	64	5 4	85	1010	65	54 1
4	1500	1340	9 7	80	6 6	85	1008	49	53 6
5	2000	1250	8 4	75	7 3	81	1008	46	53 3
6	2000	1730	10 4	98	8 2	89	1007	63	53 1
7	2000	1360	9 8	94	7 9	80	1008	25	53 1
8	2000	1540	9 9	94	7 9	74	1007	28	52 7
9	2000	1400	9 9	96	7 9	72	1009	17	52 4
Addition of 12 Grams Nacl to Daily Diet									
10	2000	670	10 1	1 08	8 8	42	1018	1 06	53 2
11	2000	510	9 6	1 21	10 3	50	1026	2 26	54 2
12	2000	980	11 2	1 32	9 7	88	1018	4 64	54 6

*Weight at commencement of experiment, other weights are those obtained at close of each subsequent twenty-four hours

The loss of weight was less than in Sawyer s case   The reason is evident, because in the few days preceding the experiment the salt in the diet had been restricted, and during this period the weight fell about 1 kg   On the morning of the tenth day the weight was 52 4 kg   Coincident with the administration of salt this rose in the following seventy-two hours 2 2 kg   Corresponding to this increase in weight was a retention of water by the body which is at once manifest by the diminution in the urine during this period

The average quantity of nitrogen eliminated in the urine per day in Taylor's experiment was 10 04 gm , in Sawyer s 11 2 gm , and in Smith's experiment 9 99 gm   The closeness of the three results is of considerable interest because of the difference of weight of the three individuals, Dr Taylor weighing 80 kg, Mr Sawyer 80 kg and Mr Smith 55 kg The case of the establishment of nitrogenous equilibrium on the same

diet for these different weights is, of course, well known, but ever striking The absorption of protein in Smith's case, as in Sawyer's, was excellent The addition of salt to the diet increased the elimination of nitrogen in the urine, despite its smaller volume, by 3 per cent, but this is a quantity too small to be of significance This observation corresponds to the more recent views on the action of salt on nitrogenous metabolism

TABLE 5 —METABOLISM IN EXPERIMENT ON DIABETIC PATIENT

Day	Vol c c	N gm	NH₃ gm	Urine Total Sugar gm	Total Carb gm	NaHCO₃ gm	Carb Bal gm	Cl
1	1200		1 4	34	96	16	+62	
4	3000		2 8	66	134	16	+58	
5	4440		3 6	142	158	16	+16	
9	4900		3 4		91	32		
11	4740	23	1 2	119	70	24	—49	2 0
12	5520			166	83	20	—83	
13	3930	25	1 4	157	73	16	—84	
14	3180		1 1	102	48	16	—54	
15	3330	27	2 3	107	38	16	—69	1 03
16	3510		2 4	133	38	16	—95	
17	3120	23 6	2 7	119	35	16	—84	0 38
18	3180	22	3 2	102	30	20	—72	0 39
19	2400	17	2 4	72	50	20	—22	0 79
20	5280		3 3	116	20	20	—96	2 56
21	2100	10 8	1 9	63	44		—19	1 53
22	5910	25 8	3 7	100	52		—48	7 93
23	5280	23 5	4 1	106	17	8	—89	3 84
24	2400	17 3	3 1	77	38	16	—39	3 48
27	2700	17 6	0 6	76	50	12	—26	5 25
30	3360		2 3	54	40	8	—14	
62	1560			0	69	0	+69	

The absolute amount of ammonia rose slightly as the experiment advanced, but for this we have already given a partial explanation On the twelfth day of the experiment (following the addition of 12 gm of salt to the diet for three successive days) the amount of ammonia was greater than the quantity of ammonia obtained by Taylor on the last day of his experiment Any lingering doubt as to the slight increase in ammonia obtained by Taylor on the last day of his experiment being dependent on the diminution of chlorin in the diet was thus dispelled

While we were engaged in this work a patient with diabetes came under our observation, whose diet by chance contained an extremely small amount of salt The case presented at first a mild form of diabetes with diffuse nephritis, but during a febrile attack the positive carbohydrate balance of 60 gm changed to a minus carbohydrate balance of the most intense type On the thirteenth day of observation the quantity of sugar in the urine was 157 gm, while the diet contained only 75 gm

carbohydrates, thus giving a minus carbohydrate balance of 82 gm This is about the maximum quantity of carbohydrates which could be formed out of the protein metabolized on this day, which was 25 gm nitrogen (X 6¼) 156 gm From this quantity of albumin it is customary to consider that (156 x 60) 94 gm carbohydrate can be formed Despite the severity of the case, the acidosis was only moderate, and on this day there was but 1 4 gm ammonia [6]

It is true that 16 gm of sodium bicarbonate were administered in the twenty-four hours, but as is well known, such a quantity will lower the ammonia only about 20 per cent On the eleventh day of observation the chlorin in the urine was 2 gm , on the fifteenth day, 1 03 gm on the seventeenth day, 0 38 gm , and on the eighteenth day, 0 39 gm On the following day it began to rise as the low chlorin was discovered and salt was added to the diet The observations made on this patient do not favor the view that a small quantity of salt in the diet of a diabetic patient increases the tendency to acidosis because the general condition of the patient was better on the days with low chlorin excretion than in either the preceding or following periods, and the actual acidosis as measured by the excretion of ammonia was not notably affected We would not attach too much significance, however, to this observation, because the excretion of chlorin may be variable even in the presence of a mild nephritis The data of the case are recorded in Table 5 It is of interest that on the sixty-second day there was again a positive carbohydrate balance of 69 gm

CONCLUSIONS

The results of our experiments on two individuals placed on an ash-free diet for periods of thirteen and nine days, respectively, show no marked changes in metabolism They simply represent the withdrawal of accessory salts from the body They confirm the views of earlier writers, that it is practically impossible to diminish the chlorin of the body by more than 10 to 14 per cent and that the loss of water is proportionate to this No remarkable symptoms appeared and those that

[6] Such a severe case of diabetes with so slight an acidosis suggests a pancreatic origin as described by Bingsch (Therap d Gegenw , 1906, p 337) and Hirschfeld (Berl klin Wchnschr 1905 xlii 1609) No support for this opinion is furnished by the analysis of the feces which was made for me by Dr F B Talbot Total feces, 360 gm total dried feces 20 758 gm Percentage nitrogen, 4 2 per cent neutral fat 1 0 per cent fatty acid, 3 9 per cent , soap, 5 2 per cent , total fat 11 per cent Total nitrogen in feces 0 871 gm Total fat in feces 2 283 gm

occurred were rather less than would be expected from such a diet, even though it contained a normal quantity of salts   We do not feel that they afford a basis for any far-reaching deductions as to changes in metabolism, and they certainly give no support to the view that the withdrawal of salts from the diet will cause an acidosis of the acetone variety   Clinical observations on the effect of the diminution of salt in a severe case of diabetes are in harmony with our experiments

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THE INHIBITION OF PANCREATIC ACTIVITY BY EXTRACTS OF SUPRARENAL AND PITUITARY BODIES *

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In a recent publication[1] we had the privilege of considering at some length the question of the activation of the pancreas by secretin, with especial reference to malnutrition and diabetes

In it we pointed out, among other things, that in some animals, especially those which are carnivorous and are not provided with grinding molar teeth, in which animals there must, therefore, be either a large amount of acid gastric secretion or a high degree of acidity within the stomach, there was evidence that pro-secretin is present in the intestines in quantities larger than are found in human beings We also reached the conclusion that the evidence to date for the absence or deficiency of pro-secretin as the cause of some cases of diabetes and malnutrition was insufficient

These were our main findings as far as the present communication is concerned, but the experience gained in these connections led us to experiment further The question of the relation of the pancreas and its evident activity, when excited by secretin, to digestion in general and to other organs in particular, is a very wide one, and, as we ventured to point out, offers a most promising and relatively unexplored field for research It occurred to us that with a definite and sure method of activating at least the "external' secretion of that gland, and with an experience equal to measuring and interpreting its response, we had at hand a means whereby its correlation with other organs might be studied

In his Harvey address[2] Starling says "Secretin may be taken as a type of a whole group of chemical messengers, which, formed in one organ, travel in the blood stream to other organs of the body and effect

correlation between the activities of the organs of origin and the organs in which they exert their specific effect" This effect, he says, as a deduction from many observations in this connection, is not due necessarily to the formation of a special substance which shall exert a specific influence on some distant organ, but possibly to the development in that distant organ of a specific sensibility to the common product of the first organ The chemical adaptations which Starling considers and of which we know most, have resulted almost exclusively in increasing the activity of the responding organ "We can not, however, draw sharp lines between the reactions involving increased activity or dissimilation and those which involve increased assimilation or growth, since, under physiologic circumstances, the latter is always an immediate consequence or accompaniment of the former"

Some unknown function of the pancreas by virtue of which it seems to have a close relation with diabetes has long been recognized, chiefly from von Mering and Minkowski's well-known observation, that extirpation of the pancreas causes glycosuria As is well known, many agents may cause glycosuria when injected intravenously or otherwise given, for example, isotonic salt solution injected intravenously in large amounts, interference with the supply of oxygen, etherization, and, lastly and more specifically, adrenalin injected subcutaneously Whatever the mechanism by which these agents act the last one named does so by producing a true hyperglycemia Now the fact, on the one hand, that a small excess of suprarenal substance in the circulation of an animal, its own suprarenal glands being intact, produces glycosuria, and, on the other hand, that extirpation of the pancreas produces a like result, suggests an antagonism or balance of action between these two organs in particular which might profitably bear investigation A relation of this kind has been suspected, though full experimental evidence has been lacking to establish it Thus, Herter has shown that painting the pancreas with adrenalin causes glycosuria, but whether this is merely a feature of its action when injected subcutaneously or intravenously is not yet known G Zuelser[3] has advanced some ideas as to the interrelation of the adrenals and the pancreas To quote his own words, he makes "the assumption that the secretion of the suprarenals is normally neutralized by the pancreas and that, therefore, the 'pancreatic diabetes' of Minkowski, which follows extirpation of the pancreas is really a suprarenal diabetes' He also claims that by injecting simultaneously

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3 Zuelser, G · Berl klin Wchrschi 1907, xliv 474

suprarenal extract and pancreatic juice, no glycosuria results   Pfluger[4] has shown that extirpation of the duodenum in frogs causes glycosuria (It is from the duodenum, of course, that the pancreas normally obtains the stimulus for the discharge of its external secretion at least)   Ehrman[5] has found that this extirpation does not cause glycosuria in dogs   but Pfluger criticizes Ehrman's work on the ground that the separation of the pancreas from the intestines was not complete and that the animals did not survive the operation for a period long enough to make the experiments conclusive

It was, therefore, with the basal thoughts just suggested that we sought to investigate the influence of various factors on the one gland of the body whose excitation by "hormones" can be induced at will, as a basis for inquiring into that further interdependence of organs which we know exists   Our first thought was to look within the body for factors which might have some effect, though the question of outside influences, such as "drugs," is an important one of itself

We attempted, therefore, at the start, to influence in dogs the flow of pancreatic juice when excited by secretin, with intravenous injections of adrenalin chlorid, taking 3 c c   at a dose[6]   Three c c   of adrenalin was sufficient instantly and markedly to increase the blood pressure, without evidently injuring the animal during the period of observation and in a few minutes the blood pressure fell again to normal   so that the dose could be several times repeated

We found on injecting adrenalin chlorid that the flow of pancreatic juice was almost at once inhibited and in most cases absolutely so   With injection of fair amounts it was at all times slowed proportionately to the size of the dog and the activity of his pancreas   Moreover, the simultaneous injection of secretin and adrenalin resulted in a total absence of flow , and furthermore, the injection of adrenalin a few moments prior to the injection of secretin prevented a flow   Occasionally   if the gland were very active and the dose of adrenalin moderate, a slight response to

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4 Pfluger   Arch f d ges Physiol 1907, cxx, 227

5 Ehrman   Arch f d ges Physiol , 1907, cxx, 295

6 The secretin we used was prepared from normal dog intestines   The animals on which we experimented were all dogs   They were kept under profound ether anesthesia and at the end of the experiment were killed   The amounts of secretin injected were 10 c c of solutions made from 300 to 400 c c   0 4 per cent HCl   This quantity of acid was found well adapted to the extraction of mucosa from the upper four feet of dog intestines, and served for numerous observations making a total of about 150 to 200 c c of secretin solution   The details of preparation are otherwise as given in our previous article (THE ARCHIVES INT MED 1908, i 231)

flow would occur late, as though, in the end, the action of the secretory factor had preponderated

In considering the matter, one of our first thoughts was, of course, that the inhibitory power of adrenalin was due to its blood-pressure-raising principle, notwithstanding the fact that changes in blood pressure are well known to have little influence in the output of most glands, and that the pressure in the secretory duct of such glands may, without much effect, be higher or lower than that in the vessels supplying it This is well illustrated by numerous long-established experiments on the salivary glands As a matter of fact, however, the injection of secretin is followed by an immediate and pronounced fall in the blood pressure The blood-pressure-lowering element of secretin is probably purely incidental, as shown by Bayliss and Starling, and, as can be seen from our records, is a feature of many extracts of tissue because of various elements present Further, under some circumstances, after the injection of adrenalin of known vasomotor activity, the blood pressure has for various reasons failed to rise very much, and again, after adrenalin injections, secretin has greatly reduced the blood pressure to a point much below normal, and yet no flow has resulted in either event, showing conclusively that this action is not the result of high blood pressure Further, the simultaneous injection of both agents frequently results in such an antagonism of the elements which affect the blood pressure that no change in its level occurs and still no flow appears We shall later refer fully, after considering further experiments, to some results obtained with old solutions of adrenalin which had undergone changes whereby they lost their property of preventing pancreatic flow, but yet powerfully raised the blood pressure A flow, therefore, took place with the blood pressure raised almost to a maximum by adrenalin More direct experiments to this end can be conducted with difficulty, as no other known substance raises the blood pressure to a degree at all comparable with adrenalin

That this inhibition of secretion is not a feature of any general action of adrenalin is shown by a number of observations, the results of which are summarized as follows by Cushny [7] "The secretion of the salivary gland and of the mucous glands of the mouth and throat is increased, apparently through stimulation of the nerve terminations, as under pilocarpin The secretion is arrested by atropin, but can be reinstated by larger amounts of suprarenal extract, which is a more powerful antagonist to atropin than pilocarpin The lacrimal gland and the bile

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7 Cushing, Arthur R Pharmacology and Therapeutics Lea Brothers & Co, Philadelphia

are also increased " Speaking of the blood pressure, he says "This active principle exists only in the medulla of the gland and, therefore, does not represent the whole function of the organ, in all probability "

It may be well here to mention the methods by which we recorded the observations which appear later In our previous work we measured pancreatic activity by registering with a watch the exact moment at which the flow of juice through the canula in the duct of Wirsung passed definite graduations marked along the canula This method was accurate enough, but not at all graphic and was, as well, voluminous in reproduction, so we had recourse to the following method

The blood pressure was recorded on a kymographic drum by means of a manometer in the femoral or carotid artery, and the respiration by a manometer introduced into the trachea By means of the electric push-button connected with the pen drawing the base line on the drum, it was possible by watching the flow of juice through a graduated canula placed in the duct as usual, to record in vertical and momentary elevations of the base line the exact moments at which the juice flowed past any given division

In order that the record of an experiment, which often covered a period of several hours, might be made continuous, we made use of a modification of the well-known "endless roll," a method which had for our purpose the advantages of recording the blood pressure in all its variations from the normal established at the beginning of the experiment [8]

The experiments above recorded of the action of adrenalin were repeated a great many times and, as our tracings show, with almost invariably the same results The amount generally used was 3 c c of the "adrenalin chlorid" of Parke, Davis & Co which is said to contain two and one-quarter grains of chloretone to the ounce In order to obviate the possibility of the latter preservative being a factor we prepared several chloretone solutions of different strengths, one of over twice the strength in which it occurs in adrenalin, but no inhibitory effect could be observed from it We next made up a solution of pure adrenalin from the dried active extract of the suprarenal glands also on the market This is said to contain no preservative of any sort but a solution made from it of the same strength as that containing chloretone again gave the same results Finally we made a suprarenal extract of our own, from the suprarenal glands of thirteen dogs on which various surgical

8 We are under great obligations to Prof E T Reichert for his kindness in devising the simple and effective kymograph which proved so perfect for the use of the endless paper roll We are further indebted to him for assistance in many technical points

operations had been performed some weeks previously in the course of experimental surgery at the University of Pennsylvania These animals were in good health and were all killed by gas at the same time for autopsy study, advantage was taken of this fact to obtain the suprarenals The glands were run through a hash machine and the resulting mass ground up with sand and about 30 c c of normal salt solution in a mortar for about fifteen minutes till the whole was reduced to a uniform pulp Salt solution was then added to a total of 78 c c and the mortar contents strained through unbleached muslin This preparation was opaque, white and cloudy in appearance, and our observations show that to all intents and purposes it had all the properties of that put on the market in regard to both blood pressure and inhibition of pancreatic flow On an earlier occasion we made a normal salt solution extract from the two suprarenals of one dog and added to it 1 c c of a saturated solution of chloretone This preparation was also active in all respects

In order to establish any peculiarity or specificity of action in this connection, however, it was then necessary to utilize other glandular extracts and other substances in the same connection

To this end we experimented with as many animal extracts of known activity as could be obtained There are, of course but few such, and there is only one of any definite therapeutic value, viz the thyroid A tablet of dried thyroid extract (the therapeutic dose for an adult human being) was ground up in a mortar and the powder rubbed up with 10 c c of water The liquid assumed a brownish color, indicating some solubility of the substance, but for the greater part this injection consisted of a fine suspension A solution of thyroid extract was also made by treating the mashed and ground pulp of two sheep thyroids with slightly more glycerin than was sufficient to cover them This was allowed to extract all night and then diluted one-half with water, strained and used in various amounts for injection There can be no question that this preparation contained much of the peculiar colloid thyroid elaboration, because the slightest amount gave the characteristic viscid reaction which occurs when the latter is treated with alkali The glands used in this instance were taken from fresh material obtained from the abattoir and used at the University Hospital in the treatment of a case of myxedema which was improving rapidly We also tried a liquid preparation of thyroid extract distributed by the manufacturers All of the above thyroid extracts however, were without influence on the flow of juice

It has been shown by Schaffer and Oliver and others that the pituitary gland contains a substance which acts somewhat analogously to the active principle of the suprarenals, in that it raises blood pressure It does this to a degree less than the latter, though the effect is said to be

continued somewhat longer   We attempted next, therefore, to obtain an
extract of the pituitary body, and used first a liquid preparation said to
be of the infundibular portion, distributed by Parke, Davis & Co for
experimental clinical observation   In answer to some questions addressed
to them by letter, the manufacturers of this solution state that it con-
tains 0 5 per cent of chloretone   Taking the same dose of this that we
used of adrenalin chlorid, we injected it after exciting the flow by secre-
tin and obtained almost the same consequences as followed the use of
adrenalin   In other words, the pancreatic flow was at once cut short and
generally completely inhibited   In nearly every instance the rise in blood
pressure was considerably less than is witnessed after the same dose of ad-
renalin, and, moreover, it was less abrupt, though the longer continu-
ance noted by some observers was not so apparent   Notwithstanding its
evidently inferior activity in respect to blood pressure, its inhibitory
action on pancreatic juice seemed to be more marked   The cessation
was in most cases more prompt, and on several occasions a second injec-
tion of secretin failed to excite a response after an interval of time fol-
lowing the injection of pituitary extract such as would probably have
insured a flow, even though slight, had adrenalin been used, showing
apparently that this preventive action sometimes lasts longer in the case
of the pituitary gland   That this feature in no way depends on an in-
crease in blood pressure is better illustrated by the pituitary than by the
fresh adrenal extracts, since the former on many occasions fails to raise
the blood pressure and more frequently the rise is so slight and so tem-
porary as to be of evidently little consequence   In this respect of raising
the blood pressure, the pituitary extracts used by us were by no means as
constant or reliable as those made from the suprarenals

On varying the time of injection, as we had done with adrenalin,
and giving the extract after excitation of the pancreas by secretin, then
before its excitation, and, finally, with the injection of secretin, we met
with nearly identical results   In both of the latter instances the flow is
prevented by the dose mentioned (3 c c), and in the former it is greatly
slowed and generally promptly stopped   In regard to both the adrenal
and pituitary extracts it is noticeable that their action is apparently
more marked when the injections precede or are coincident with the
injection of secretin than when they follow it   Sometimes with a very
active pancreas the initial dose of adrenal or pituitary would be insuffi-
cient to retard very much a violent response to secretin but we found
that if given before the injection of secretin the flow was always in-
hibited

The commercial extract of pituitary gland which we first tried (the
exact nature of which was of course entirely unknown to us) was open

to the same theoretical objection as adrenalin, and it was possible that methods of preparation or the preservatives used in its manufacture might conceivably produce these effects or modify in some way its own properties, indeed, they might actually disguise those with which we were concerned We, therefore, determined to prepare our own extract, which we did as follows

On the occasion mentioned above, when thirteen dogs were killed, we removed separately both portions of the pituitary gland, nervous and glandular This procedure is relatively simple in the dog, as the organ is easy of access and is exposed to view as soon as the frontal lobes of the brain are raised The nervous part in the dog is a small white globule about the size of a grape-seed, and on being crushed extrudes a slightly viscid juice which can be rubbed into a paste To the thirteen infundibular portions so treated we added 30 c c of normal salt solution, agitating the whole for some time to insure as complete extraction or solution as possible The resulting fluid contained very little residue of any sort and was transferred directly to a small sterile Erlenmeyer flask The glandular portion of the pituitary was then treated in the same way with an equal amount of salt solution and transferred to another flask It might be mentioned here that, while histologically the glandular portion of the pituitary body is epithelial tissue, it in no way resembled a gland macroscopically, and by the uninitiated eye would be taken for the nervous element On being crushed it resembles so much fairly dense tissue and gives a solution more tinged with blood than the nervous extract, which is almost white in color

The extract from the nervous portion of the pituitary was active in regard both to blood pressure and to the suppression of the pancreatic flow, agreeing in all respects with the other preparations tried The dose used was 10 c c of extract, which was equivalent to the nervous fraction of about four and one-third whole glands The blood pressure was raised to a degree somewhat less than was seen after most of the other pituitary injections, but this may well be accounted for by the strength of the preparation, which must have been considerably lower in actual extractive content than the commercial article, which is made from the organs of larger animals

The extract from the epithelial portion of the pituitary was injected without any evident effect on either the blood pressure or the flow of juice, which is quite remarkable, considering the immediate contiguity of the structures, and argues much for a specificity of action We shall have more to say on this subject later

Having satisfied ourselves that the pituitary and the suprarenal both contain something whose action on the pancreatic flow is marked, it remained now to investigate other tissues The one of known physiologic interest as regards its therapeutic action we had already tried with a negative result, but it could not be postulated that other organs or other tissues might not contain some principle which would act analogously Consequently we made extracts of the parenchyma of other glands and of other nervous tissue Of the former the epithelial portion of the pituitary already served as a striking instance About one-fourth of the liver of a freshly killed dog was put through a hash machine and then ground with sand and a small amount of normal salt solution in a mortar until a fairly uniform mass resulted More normal salt solution was then added, making a total of 150 c c used, and the whole agitated and ground in a mortar as well as possible for about twenty minutes It was then passed through unbleached muslin to free it from sand and tissue residue and then transferred to a sterile Erlenmeyer flask

In addition to the above, on another occasion, a glycerin extract of liver was made by adding about 150 c c of glycerin to the mass passed through the hash machine as recorded, and after agitation and pressure in a mortar the whole was allowed to extract for twenty-four hours A small amount of water was then added and the mass strained Another watery extract had been previously prepared and this procedure was repeated only because it was thought that an unavoidable delay of some hours might in some way have impaired the activity of the first With the exception just noted, the glandular extracts of our own preparation on which we based conclusions were all made within a few hours of the death of the dogs and injected within a few hours at latest after their preparation [9] None of the liver preparations seemed, however, to have the slightest effect on the flow of juice, though the blood pressure was sometimes considerably lowered, as has been shown by Halliburton, Dixon and others to be the case with several organ extracts

We next experimented with nervous tissue, for which purpose we obtained the brain of a freshly-killed dog, passed it entire through a hash machine and then ground the pulp in a mortar with sand and a total of about 130 c c aqua distillata Distilled water was used inadvertently instead of normal salt solution, as in the other experiments

While the subject of the depressing effect of extracts of nervous tissue has already been pretty thoroughly studied by Halliburton and others, it

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9 The animals were killed between 6 and 7 a m The suprarenal and pituitary glands removed between 8 and 10 a m , and extracts made by noon They were injected during the afternoon and evening of the same day

is interesting, apart from their relation to pancreatic activity, to compare the systemic effects produced by injections of this last preparation with those of other extracts The amount of fresh liver substance taken for extractive purposes was about one-quarter of the organ, to which was added 150 c c of extracting fluid The brain of a medium-sized dog compares closely with this in bulk as well as in percentage of water We macerated the brain with 110 c c of extracting fluid, so that bulk for bulk the solutions were approximately equal, putting aside the question of their respective yields on attempts at extraction The first dose of brain extract used was 10 c c and with a slight fluttering and preliminary rise of blood pressure the dog almost instantly died The doses of liver and other tissue extracts were 10 c c and more The next dose of brain extract was 5 c c, and with a marked fall of blood pressure this animal died at once, though nothing had been previously injected into him The next dose administered was 1 c c of extract in 10 c c H$_2$O, and again a fresh animal at once died, and finally we injected 0 25 c c diluted with 10 c c of water, and though the blood pressure fell alarmingly and it seemed by the cardiac inhibition and small excursion of pulse that this animal would also succumb, the blood pressure rose again and the animal seemed to recover However, after one or two injections of secretin and adrenalin, which had been well borne in nearly every other instance, this dog also suddenly died, apparently from injury due to the first injection

It is interesting to note that, notwithstanding the powerful and almost lethal effect of even a small dose of the watery extract of brain tissue, absolutely no effect could be detected on the flow of pancreatic juice, which continued, as we had frequently observed before, when the animal was moribund

That the inhibitory action of the pituitary is therefore not a function of nervous tissue in general is clearly seen, because the mass of the brain as compared with that of the diminutive pituitary bodies is very great, and the effect of its extract, if potent, should be both actually and relatively greater Moreover, the pituitary gland and brain substance are, of course, in the most intimate contact, and were this activity of the hypophysis common to other higher nervous tissue it is almost inconceivable that it should be so sharply differentiated in our work Whether every part of the brain would act similarly in extract, or whether in such a gross method of extraction we have diluted, beyond evident potency, tissues from other active regions, is problematic

In view of the relation which the pituitary is supposed to bear to the testes, as evidenced by those cases of acromegaly in which a lesion is dem-

onstrable in the hypophysis, and testicles also, it seemed advisable to try the effect of extracts from testicular tissues, although the immediate physiologic effect of these on the circulation and economy in general has been extensively studied by Dixon   We macerated two dog testes freed of their epididymes and then ground them up as before, with sand and mortar, finally adding a total of 78 c c of normal salt solution   The whole was then meshed through linen and injected in the usual manner but no effect on the flow of juice was noticeable, whatever the time of the injections   .

Our purpose in making glandular extracts of our own was two-fold In the first place, such a procedure was necessary to give us the material we needed to widen the scope of our work, and, in the second place it seemed advisable to test whether, by the methods we used, we could extract the features of certain glands which are known to be present in them   Failing in that, it could hardly be assumed that we were capable of extracting the active features of other parts, but if, on the other hand we were successful, it could be reasonably believed that in the tissues under consideration no active substance was present, or that, if present, it was not susceptible of extraction by these methods   We desire to be understood, therefore, as claiming, not that this observed antagonism of action is one positively peculiar to two organs alone, but that it is one manifested by them under certain conditions of treatment and a property which we have been unable to extend as yet to other tissues   That a certain degree of specificity is probable from the evidence now at hand must be granted   Whether further observation will corroborate or disprove this it remains for the future to show

We also experimented with atropin   According to the physiologists atropin depresses or suppresses practically every secretory activity in the body except that of the kidney, and possibly the pancreas   On the flow of pancreatic juice, however, we were unable to perceive the slightest effect from it   The amounts administered were nearer the physiologic limit for a dog than were the doses of adrenalin, which can be repeatedly given in quantities of 10 c c at a time, in the form of the commercial adrenalin chlorid without much evident injury   Our records show that one of our dogs received 1/300 gr atropin sulphate followed in a few minutes by another dose of 1/300 gr without evident result on the flow whereas another fresh dog died from what resembled paralysis of the respiratory center apparently as the immediate result of an injection of 1/150 gr   Atropin neither prevented nor stopped the flow of juice

Efforts were also made to simulate with digitalis the rise in blood pressure produced by adrenalin and pituitary extract, but no effect of any value could be obtained in this connection

Now it is true that to speak of making an extract of so highly organized and differentiated a structure as the liver, not to mention the brain, seems crude, but it is also true that in considering such a problem as we have here we must first begin with the lowest terms and with such methods as are compatible with our knowledge of the subject Having found in two organs some active substance which can be extracted by their treatment with salt solution, we are driven to applying the same methods to other parts of the economy if we would learn more of its extent and distribution It can well be urged that in different sites the same property or different properties require different methods of extraction, and that treatment with water or glycerin in one instance will not effect the same result in another Nevertheless, we have indubitable proof that both water and glycerin can extract certain of their activities from several organs, as, for example, the suprarenal and thyroid glands respectively, and we also have equal proof that from other regions of the body can be derived substances of such toxicity that an animal subjected to their action immediately succumbs Just which of their numerous ingredients are responsible for these properties we are often unable accurately to say, and it is even a disputed point as to what factor in the extraction of nervous tissue produces the profound depression of the vascular system which is followed by death That the same methods of attack, under such circumstances, should therefore necessarily appear superficial and crude follows perforce When we consider how easy of extraction by almost identical means is that principle of the adrenals with which we are most familiar, namely, the blood-pressure-raising element, it seems astounding that its discovery should date from a period so recent as 1894, and if it be borne in mind that such methods in that instance furnished striking knowledge and that we have progressed little since then in our knowledge of the functions of the suprarenals themselves, the methods necessary in dealing with such an unknown subject appear less general and more definitely specific

We hope to be able to investigate this antagonism of action, after separating the pancreas from its nerve supply, as thoroughly as possible, since it may well be that the effects noted result from the mediation of the sympathetic system It is of some interest to consider here briefly a few points in the morphology of the suprarenals and the pituitary in their relation to our observations It has been shown[2, 7, 10] that the

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10 Dixon Jour Physiol, Cambridge, 1900 1901, xxvi

classic effects of adrenalin are produced in large part by its action on the sympathetics, and wherever we test its action, in respects other than those under consideration, we find the results identical with those obtained by stimulation of this system of nerves and ganglia The suprarenals are derived morphologically from two sources, the cortex coming from the mesoblastic tissue and the medulla from a direct outgrowth of the sympathetic system As evidence of the latter we find in many of the lower orders distinct nervous tissues consisting of neuroglial cells, which are, however, harder to differentiate in man, indeed, in certain forms, viz , teleostean fishes,[2] the two parts, medulla and cortex, remain separate through life Now, an interesting corollary to our observed analogy of action between the suprarenals and the pituitary is the fact that morphologically we could reasonably conceive of these two organs as having something in common The pituitary body, like the suprarenals, consists of two parts, and again like the adrenals, each part has a separate derivation The anterior lobe has its origin from one of the branchial clefts in a pouch of buccal mucous membrane [11] The posterior is derived, like the medulla of the adrenal, from the ectoderm It comes from the floor of the third ventricle, to which it remains attached by a stalk, viz , the infundibulum According to some, the larger anterior lobe has two sources, the primitive oral tissue in early life and the anterior portion of the alimentary canal [12] Wiederscheim[13] says that "the secretion from the pituitary gland formerly passed into the ventricles, and one of the more recent theories assumes that the pituitary corresponds to the primitive mouth (palæostoma) of the proto-vertebrata, which to a greater or less extent is represented by the combined impaired nasal and pituitary passage of cyclostomes " In certain mammals there can yet be seen evidences of the passage which connected the anterior part with the posterior part and thence with the third ventricle [11] These facts by themselves are of interest, and in connection with our observations they are not in discord That an organ so anatomically remote as the pituitary should have a definite influence on a gland in possible morphological relation to it is therefore less surprising

As with the adrenals, it is that part derived from the nervous system which gives rise to the blood-pressure as well as the inhibitory element For neither the epithelial portion of the pituitary nor the cortex of the suprarenals, however, is there any recognized function The two parts

11 Herring   Jour Physiol Cambridge, xxxii No 6
12 Stengel   Text Book of Pathology, Philadelphia Saunders, 1906 Davidoff, Bohm   Text Book of Histology, Huber 1900 p 380
13 Wiederscheim   Comparative Anatomy of Vertebrates Parker 1897, p 155

of the pituitary can be worked up and extracted separately, as noted above, but this has not yet been possible with the adrenal, so far as its inhibitory action is concerned, although from the suggestive analogies between these two organs and the very evident limitation of the inhibitory feature of the pituitary to its nervous moiety, it seems probable that the adrenalin inhibition has the same point of origin as the blood-pressure factor, viz, the medulla, still, this can not be postulated at present, and it may be, indeed, that we have here an expression of one of the functions of the suprarenal cortex

Since the completion of our experiments some work has been reported by Botazzi, D'Errico and Jappeli,[14] in which they obtained an inhibition of flow from the salivary gland by painting it with adrenalin Stimulation of the chorda tympani then failed to give a response Without questioning the accuracy of their findings, which are at variance with the work quoted by Cushny, the question as they present it does not argue an inhibitory action on the salivary gland analogous to that observed by us on the pancreas In the first place, they are dealing with a gland excited by purely nervous means and not by a chemical substance which reaches it through the blood Again, and more important, the inhibited salivary gland is stated by the above Italian workers to be in the highest degree anemic after local application, a condition in which it is hard to conceive of its having an activity of any sort, since it is for the time being out of commission This is of course, in no way comparable to the action of adrenalin on the pancreas (if its action *is* on the pancreas) when the flow of juice in the latter organ is inhibited by a systemic injection into the jugular vein And, furthermore, this view of the matter does not explain the action of the pituitary which has, as far as we know, no such reported action on glands Finally, to ascribe to an ischemia of the pancreas the inhibition of pancreatic flow after jugular injection of a small dose of adrenalin, supposes that most or all of the organs of the body become anemic to such a degree that they can no longer act, which is stretching a hypothesis beyond the facts to support it

It is somewhat immaterial, however, whether adrenalin acts on the pancreas alone or also on other organs, since the point of interest is that in affecting it at all in this way it affects the one gland of the body whose connection with diabetes is best established That it might also affect certain other analogous structures with inhibition would not be surprising, though the evidence now is against it

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14 Botazzi, D'Errico and Jappeli Physiol Inst Univ , Naples Biochem Ztschr , January, 1908 vii, 431

One feature of our work demands some notice and is of suggestive interest On the day when we experimented with the pituitary and suprarenal extracts of our own manufacture we made our first injections about 1 p m The preparations used for this purpose had been made between 10 a m and 12 m from the animals killed early that morning as noted The samples of suprarenal extract first injected were vigorously active Because of press of work under the desire to utilize our preparations before they were affected by decomposition, we were unable to use the pituitary extracts before evening, about 8 p m Although tried then for the first time, about eight hours or more after their manufacture, they acted vigorously, as stated On endeavoring to repeat with the suprarenal extracts our work with them of the early afternoon, however, we were able to get no inhibitory action, although the blood pressure was still raised To control this conflicting observation we tried a preparation of adrenalin made some weeks previously from the dried extract of the suprarenal gland put on the market by Parke, Davis & Co in small grain vials and said to be free from preservatives This solution corresponded purposely, in adrenalin strength, to the usual commercial article containing the preservative chloretone It was remarked by one of us immediately prior to the injection, while filling the syringe, that the solution showed a slight mould It had been used many times before and had in every instance been powerfully and emphatically active, though there had been a lapse of perhaps a week since its last use To our surprise, this preparation raised the blood pressure decidedly, but was absolutely without influence on the flow from the pancreas We then tried an injection of the commercial adrenalin chlorid solution, also some weeks old but containing chloretone, which both raised the blood pressure and inhibited the flow, as we had repeatedly observed before

The absolute significance of these observations can not be established until we repeat our experiments in this particular connection, but the most obvious and reasonable deduction is that the extracts from the suprarenal glands contain two or more substances, one of which acts on the blood pressure and one of which acts to inhibit the flow of juice The former of these seems the more stable of the two and resists decomposition for a considerable time but the latter loses its activity very shortly, perhaps in a few hours In the instance of the preparations of our own manufacture from dog organs the tissues and the extracts from them were, of course, contaminated from the start with the ordinary postmortem putrefactive agents, and in order in no way to impair the efficiency of the extracts no attempt was made to introduce preservatives or sterilize them The dried extract of the gland however, was presumably

sterile to start with and the solution made from it remained fairly free from infection except in so far as it was contaminated by the initial weighing of the dry powder Sterile salt solution was added to this and the solution kept on ice in a corked bottle, the only further contaminating agent, beyond contact with the air when the cork was removed, being the needle of the syringe This was always thoroughly cleansed with water after each injection, though not sterilized Under these circumstances decomposition would surely proceed rapidly from the start in the case of our dog preparations, but slowly in the case of the others We can offer no explanation for the apparently greater stability of the pituitary inhibitory factor except that the pituitary glands, being small, were easily mashed in a small agate mortar and quickly transferred to small flasks, while the suprarenals required longer and more vigorous treatment with sand in a mortar, had also first been run through a hash machine, and were hence more open to infection

The process which operated to destroy the activity of these preparations may be simply that of decomposition by putrefactive organisms, or it may be, on the other hand, of an oxidative nature more like that to which Bayliss and Starling have ascribed the slow deterioration of secretin and its more rapid loss of activity on evaporation in efforts to concentrate it All the points here suggested are yet to be worked out, however, in their relation to our work

We are by no means sure, at the present writing, of the full interpretation of the results under discussion They are but the earliest steps in a line of work on which further observations may throw much light They seem to us, however, to be very suggestive in their possible bearing on other interglandular relations, on the medium in which these are maintained, and possibly on a new conception of the interdependence of various organs now the subject of speculation For these reasons it seemed advisable to publish our results at this stage and make their further amplification the subject of later contributions

In studying the records, and indeed through a consideration of all our work, it must be borne in mind that we are dealing with a balance of power between various factors, no one of which is susceptible of exact definition or measurement As with the study of the pharmacologic action of drugs, there must be taken into consideration, besides the size of the dose, the activity of the organ under consideration, and the condition and size of the animal as a whole What may be quite sufficient markedly to affect one animal may be altogether inadequate in the treatment of another

Popielski[15] has recently taken issue with Bayliss and Starling as to the method of action on the pancreas of acid extracts of the intestinal mucosa and indeed as to the existence of secretin at all, as a specific excitor. He also claims to be able to produce pancreatic activity with extracts of stomach and large intestine. The main point of discussion in this controversy is somewhat beside our present issue, though there are a number of incidental features which have a close relation to some observations of our own.

Popielski thinks that the secretion of pancreatic juice after excitation by secretin is dependent on a fall of blood pressure and that if the blood pressure be maintained high no flow results. He uses adrenalin to raise the blood pressure and notes with the high pressure that there is no flow. He concludes also, as an incidental point, that adrenalin, in itself, does not inhibit pancreatic activity. He considers that stimulation of the pancreas by secretin and stimulation by HCl in the duodenum are different processes. Now, it seems to us that our work throws some light on several of these questions. In the first place, we have obtained some further results with adrenalin (already mentioned and to be referred to again presently). Popielski's use of it seems to have been solely to raise the blood pressure. In so doing he has apparently overlooked the other feature of it, for, while he notes incidentally that it does *stop* the pancreatic flow, he thinks this phenomenon due to the high blood pressure and not to the adrenalin proper. He specifically states that adrenalin in itself does not influence the flow of juice. Now, as we mentioned above, one of our series of experiments conclusively proves that it is possible to obtain a flow after the injection of secretin, despite the fact that the blood pressure is raised to a high point. We refer to those observations, happened on by chance, in which exposure to air and apparent decomposition had destroyed the inhibitory factor of a solution of adrenalin, but allowed the blood pressure element still to act. Whatever the true explanation of this—and we offer nothing positive on this point—it is a fact that on several occasions such a solution distinctly raised the blood pressure sometimes to a very high point and yet the juice flowed. To have noted this once would be sufficient to prove it possible. We have a number of such records. Not only does this prove that it is not the blood-pressure element alone of adrenalin which affects the flow of juice, but it also proves that, as just stated, a flow may take place following secretin when the pressure is high and that *therefore* a low blood pressure is *not*, as Popielski claims, a feature necessary to it.

15 Popielski. Arch. f. d. ges. Physiol., 1907, cxx, 451, 1908, cxxi, 239

His findings in regard to the failure of atropin to affect the flow are in agreement with ours, viz, that no inhibition results from it We have as yet been unable to effect a secretion from the pancreas by the injection of extracts of other tissues, though we have not yet tried those particular tissues (i e, stomach and large intestine) used by Popielski He states that a watery solution is sufficient to extract the exciting factor, and we used also water and normal salt solution in our work We obtained no flow, but, on the contrary, from certain tissues, as mentioned above, we obtained an inhibition We also made an acid extract of the pancreas with 0 4 per cent HCl, and treated the whole exactly as we did a coincidently prepared and active solution of secretin No flow resulted, however, from the acid extract of pancreas

It should be mentioned also that after section of both vagi we still obtained the inhibitory effect from suprarenal and pituitary extracts

Some further interesting observations have recently appeared which deserve reference Fleig[16] reports on the physiologic properties and toxicity of normal pancreatic juice and that provoked artificially He considers as normal, juice elaborated under the influence of chyme secreted through a duodenal fistula in an otherwise sound dog and then injected into the duodenum of the dog whose pancreas is under consideration The quantities of chyme required under these circumstances are considerable (20 to 30 c c) and they must be repeatedly injected (every ten to twenty minutes) to induce a proper flow The secretion thus provoked differs much from that which follows intraduodenal injections of 0 3 per cent HCl, the time required is much greater and the quantity of juice furnished "infinitely less " Under the influence of chyme thus conducted the juice remains very thick and viscid from beginning to end, whereas juices secreted after more artificial stimulation differ in this and other physiologic respects until after repeated injections of secretin For example, the pancreatic juice may have hardly any of its normal physical characters

Natural and artificial secretions also vary in their toxicity when injected into animals, the former being more powerful in this respect The lowered toxicity of secretin juices, Fleig thinks, is in consonance with their poor content of solids rather than their relative tryptic inactivity He says that the above conditions are true also in general of the biliary and salivary secretions

Now it seems to us that the above results are what might be expected That a purely artificial and foreign substance, such as secretin, full of other extraneous matter and differing itself not only in quantity but in

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16 Fleig Compt rend Soc de biol May 8, 1905 No 15

quality from the normal pancreatic excitant, should produce the same juice as does the slow extruded gastric chyme, acting over perhaps many hours, seems unlikely in the highest degree. It would, indeed, be extraordinary if the results of such varied stimulation were the same. The amount of excitant which reaches the pancreas normally from the duodenum is surely a small or moderate quantity, that which is injected with secretin is not only concentrated in preparation from many feet of gut, but is injected in a few seconds to spend its whole force at once. It is hard to see how any gland could long continue to elaborate a normal product under such vigorous treatment. We hope to investigate shortly the effect of adrenalin and pituitary extracts on the pancreatic flow after stimuli other than secretin, especially chyme from a gastric fistula in an otherwise healthy dog, but it seems probable that the principles are much the same on which depends secretion after all of these and that the results of such work will be in harmony with what we have already seen. If adrenalin and pituitary extract inhibit the sudden and violent initial flow from secretin, it is conceivable that they would also affect the mild response from other stimuli. It must be remembered that the altered nature of pancreatic juice after secretin comes as the result of protracted and powerful stimulation and not from the initial dose.

It is interesting to note in connection with our work the observations of Meyer[17] and Frouin,[18] which afford some evidence that extirpation of the suprarenals, after the induction of diabetes in depancreated animals modifies the severity of the diabetes and reduces the elimination of sugar.

We hope to concern ourselves now with the question of the site of this antagonism between the pituitary and suprarenal glands, on the one hand, and the pancreas, on the other, with the question of whether it is a chemical action, in the general sense of the word, which occurs in the circulation, or whether it is the result of some influence excited on the pancreas alone, or whether, again, it is accomplished through a nervous mechanism. The solution of these problems should give information of value in studying the influence of such factors on the so-called "internal secretion" of the pancreas, and its relation to diabetes. Whether on hypodermic injection adrenalin produces glycosuria, which it does in a few minutes by virtue of an inhibition of the internal secretion of the pancreas analogous to the inhibition of its external and visible discharge, is yet to be investigated. We have been unable to produce a glycosuria after either the subcutaneous or intravenous injection of 1 c.c. of pituitary extract. The solution used was made for us without

17 Meyer   Compt rend Soc de biol, Feb 14 1908 p 219
18 Frouin   Compt rend Soc de biol, Feb 14, 1908, p 216

chloretone by the manufacturers, but we have not as yet controlled its inhibitory activity on the external pancreatic flow and, therefore, can not be positive on this point

It yet remains to investigate more thoroughly the degree of specificity by trying the effects of other tissues and other methods of extraction, but, whatever the result of this, it appears reasonably certain that this feature to which we have called attention is one peculiar to certain structures, and from the data now available the expression of hitherto unknown properties of several organs

In conclusion, it is a pleasure and a duty to express our great obligation to Dr David L Edsall for his constant and helpful interest in the work, and we also wish to thank Dr John Marshall for many courtesies in the loan and equipment of apparatus

CONCLUSIONS

1 The suprarenal glands and the nervous moiety of the pituitary body in dogs contain something which, on extraction with salt solution and intravenous injection into dogs, cuts short the flow of pancreatic juice, after the administration of secretin   It also prevents the stimulation of the gland by secretin if its injection precedes the secretin

2 This feature has been found, to date, in no other tissues

3 It is independent of the general rise in blood pressure seen after the intravenous injection of adrenalin and pituitary extracts

4 The inhibitory factor of extracts of the suprarenal glands seem to disappear by decomposition, oxidation, or other process, before the blood-pressure raising element is gone   It would appear that the suprarenal and the pituitary bodies have at least one property other than those qualities generally recognized as present in them

1953 Locust Street

THE CLINICAL VALUE OF THE QUANTITATIVE ESTIMA-TION OF PEPSIN,

WITH SPECIAL REFERENCE TO THE METTE AND RICIN METHODS

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AND

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Beaumont's famous experiments showed that the gastric juice, even outside the body had an active solvent action on food, and this led Muller to suspect the presence in it of a substance acting like diastase on starch flour Eberle, in 1834, found this principle to be present in the acid gastric mucus Muller and Schwann found that this was true of acid extracts of the mucous membrane, but that neither acid nor extract alone had any activity Subsequent research showed that this was a property of the gastric mucus or secretion and not of mucus in general, as was originally surmised Pepsin has since that time been exhaustively studied, and many remarkable facts have been demonstrated, the most interesting of which is Schutz's law, so-called, which is that the quantity of pepsin varies according to the square of the amount of albumin digested In spite of all the effort that has been devoted to its study, pepsin, as such, has never been isolated in a pure state, so that it is impossible to estimate it quantitatively in a true sense of the word, all that can be done is to measure its effects and thus gain an idea of its concentration in a given solution

The numerous quantitative methods for the estimation of the activity of pepsin have been so frequently reviewed that it is hardly necessary to discuss the older literature at length in the present paper It will be sufficient to refer to the summaries in recent text-books, such as that of Boas, or to the articles of Koettlitz, Nirenstein and Schiff, Robin, Roth, and others The following brief enumeration is, in part, after Roth

1 The procedures of Biddel and Schmidt, Brucke, Gruenhagen Jaworski, and Herzen are methods in which the stomach contents are diluted until no further digestion occurs or in which a certain amount of albumin or fibrin is exposed to the digestive action of pepsin for vary-

ing periods of time   The amount of pepsin is calculated with reference to the dilution required or the time elapsed   Grutzner and Bourget used fibrin colored with carmin and estimated the amount of pepsin by the intensity of the red color of the gastric juice produced by the solution of the fibrin   Spriggs utilized the change in the viscosity produced by digestion as a measure of the ferment action   These methods at the best can only give approximate results

2 Klug (Van Valzah and Nisbet) used the biuret test as a measure of the albumin digestion   The elder Schutz, Oppler and J Schutz also calculated the amount of pepton formed, Schutz by the polarimetric method and Oppler and J Schutz by the estimation of the total nitrogen   Oppler used the Kjeldahl method, but surrounded his test with so many precautions to secure natural conditions of ferment action and accuracy in results that it is generally regarded as the best and at the same time the least available of all methods

3 In recent years Mette, Hammerschlag, Bettman and Schroder, Solms, Gross and others have introduced methods which aim at the exactness of the last-named procedure, combined with ease of application Solms' test is described in full below   Bettman and Schroder determined the amount of pepsin by observing the rapidity with which the foam produced by shaking up an albumin solution containing pepsin is dissolved   Some of those who have employed this plan do not appear to have been favorably impressed (Cobb)   Hammerschlag's method is too widely known to require detailed description   It is based on an estimation of the albumin in a special solution, before and after digestion, by means of the Esbach albuminometer   We have used it in a few cases and have found, as far as our limited experience goes, that the results correspond in a general way with those obtained by the Mette method

The following table illustrates a few comparative tests with the Mette and Hammerschlag tests

No	Mette	H
M 498	4 3 mm	97 per cent
M 638	3 9 mm	87 per cent
M 505	3 2 mm	81 per cent

Hammerschlag's test is generally regarded as inferior to that of Mette and possesses many faults which have been enumerated by Roth and others

The method of Mette, as modified by Nirenstein and Schiff, is generally conceded to compare in exactness with that of Oppler   The technic which we have employed is not widely different from that of Nirenstein and Schiff (cf Sahli) and was described by one of us, with Dr Sailer, a year or two ago   For the convenience of those to whom it is unfamiliar

it may be briefly described Glass tubes, 1 to 2 mm in caliber and 20 or 30 cm in length, are filled by suction with white of egg, plugged with bread and boiled for five minutes They are then sealed with sealing wax and after three days are ready for use The test is carried out as follows One c c of the gastric filtrate is diluted with 15 c c of N/20 hydrochloric acid Two sections of tubing, 2 or 3 mm in length are added A triangular file is sufficient for cutting the tubes The specimen enclosed in a covered dish is kept in a thermostat at 37° C for twenty-four hours At the end of this period the column of albumin digested at each of the four exposed ends is carefully measured in tenths of a millimeter An average of the four readings is recorded as the result, but it is usual to square this for comparison with other tests in accordance with Schutz's law

The following examples will make this clear

No	Dil	Reading	Squares	Relative Strength
P 271	1 in 4	6 8	46	4
P 271	1 in 16	3 4	11 6	1
P 273	1 in 4	6 4	41	4 (approx)
P 273	1 in 16	3 3	10 9	1

Mette's test thus modified excludes various errors which impair the value of many other methods, because it possesses the following advantages

1 The acidity in all cases is rendered approximately uniform without any tedious titrations being required

2 The dilution is sufficient to overcome inhibition due to albumoses (Sailer and Farr), etc , or antiferments

3 A uniform surface is exposed to digestion at all times

4 Numerous observations show that it complies with Schutz's law in dilutions sufficient to avoid inhibition and to prevent a digestion of more than 4 mm

Objections to the method are

1 Albumin from different eggs or albumin coagulated at different temperatures or heated for different periods of time varies considerably in digestibility

2 Differences in the caliber of the tubes beyond certain limits affect the readings

3 Wide variations in the temperature of the thermostat have the same effect

4 There is a decided personal index in measuring the column of albumin

These faults can be largely overcome by the following measures

1 An unvarying technic and the use, possibly, of artificial or dried egg albumin of uniform quality (Onuf)

2 The use of an artificial pepsin control For this purpose a 1 or 2 per cent solution of a standard pepsin should be employed, diluted 1 in 16 in the same way as the specimens to be examined

3 A uniform method of measurement

In these tests we employed an ordinary clinical microscope (low power) fitted with a movable stage and vernier scale

Two illustrations will show the value of controls where there are wide discrepancies

(a) No	Mette	(b) No	Mette
M 273	5 2	M 511	4 4
M 282	5 8	M 520	2 8
M 251	2 8	M 638	3 9
Control pepsin, 1/16 per cent 4 2		Control pepsin, 1 16 per cent 2 8	

Comparison in these cases leads us to lay less stress on the high figures obtained in the first experiment Similarly M 251 can be regarded as a case of greatly diminished pepsin, while M 520 with the same reading is merely a low normal

Jacoby, in 1906, in a short article disputing Pawlow's assertion that pepsin and rennin were identical, introduced a new method of determining pepsin, which, he claims, decided definitely the individuality of the two ferments This method was by means of ricin, a solution of which, he found, was cleared up by pepsin Although this peculiar property had been observed by him some time before while pursuing his study of ricin, its adaptability to clinical use was not brought forward until Solms published his paper in 1907

Jacoby had found that, if pepsin were added to a 1 per cent solution of ricin in salt solution, the cloudiness due to the albuminous substances in the ricin disappeared rapidly and completely Working on this under Jacoby's direction, Solms evolved the following simple procedure, the only fluids needed being a solution of ricin and a N/10 hydrochloric acid solution

The ricin solution is made by dissolving 0 5 gram of ricin in 50 c c of a 5 per cent sodium chlorid solution and filtering (The ricin used by Solms was obtained from the Vereinigte chemische Werke, Charlottenburg, Salzufer 16, costing 2 marks for 10 grams Solms preferred this preparation of ricin to Merck's, principally on account of the limited supply and the great cost of the latter) The filtered ricin solution has a somewhat cloudy appearance, but on the addition of 0 5 c c N/10 hydrochloric acid solution becomes decidedly milky The milky appearance is cleared up by pepsin

His technic is as follows   The gastric juice is obtained by extracting the stomach contents one hour after the ingestion of an Ewald-Boas test breakfast   He tests this for the presence of free hydrochloric acid, then determines the total acidity, and in appropriate cases examines for lactic acid   According to his findings he makes varying dilutions of the contents with distilled water   In cases of hyperacidity he dilutes the filtered contents from 1 100 to 1 10000, whereas in cases of anacidity or subacidity the dilutions vary from 1 10 to 1 100   In normal cases he dilutes from 1 100 to 1 1000

In each of the five test tubes he puts 2 c c of the filtered ricin solution, then with another graduated pipette he adds 0 5 c c N/10 hydrochloric acid, which causes the mixture to become very cloudy   Having numbered the test tubes 1, 2, 3, 4 and 5, he puts in the first tube 1 c c of boiled gastric juice, in the second, 0 9 c c , in the third, 0 8 c c , in the fourth, 0 5 c c, and in the fifth, 0 c c   Then he takes the unboiled juice and, having diluted 1 c c of juice with 99 c c of water, he puts in the first test tube 0 c c , in the second, 0 1 c c , in the third, 0 2 c c , in the fourth, 0 5 c c, and in the fifth, 1 c c, so that in each tube there are 3 5 c c of fluid   The test tubes are then corked and put in an incubator, where they are allowed to stand for three hours, at the end of this time they are taken out and the tubes examined to see with what dilution the ricin has been cleared up   If an incubator is not at hand the tubes can be left at room temperature, of course for a correspondingly longer time

In order to obtain a convenient expression of the pepsin content of a gastric juice, he designates that amount of pepsin contained in 1 c c of a 1 100 dilution, which is capable of clearing up the ricin solution after three hours' standing in an incubator, as 100 pepsin units   This he has decided on as the normal standard, because after many examinations of specimens of normal acidity he found the ricin to be cleared up by 1 c c of a solution diluted 1 100   Solms considers the normal acidity to be 40 to 60, and anything above or below this to be hyperacidity or hypoacidity, and gives tables showing the pepsin content in these various conditions His tables show no fixed relation between the acidity and the amount of pepsin, except in those cases in which the acidity is very low or the free hydrochloric acid entirely absent, under which conditions the pepsin will be found to be low also   Solms thinks that from a study of his tables he has learned nothing which would tend to show that the estimation of pepsin has a diagnostic or therapeutic value

Witte studied this new method of Jacoby and Solms and recommends it strongly on acount of its simplicity and cheapness   The only modification he proposes is to add a dilution of 1 50, since in his experience

theie have been cases where a dilution of 1 100 did not quite dissolve the
11cin His conclusions are about the same as those of Solms, namely,
that the noimal pepsin unit is between 100 and 200 and that there is but
slight relation between the acidity and the amount of pepsin, except in
cases of lowered acidity, in which the pepsin is likely to be lowei Witte
made a few comparisons with the Mette method, but prefers the ricin
piocedure

TABLE 1 —NORMAL ACIDITY—40 60

Serial No	Total Acid	Free Hcl	Ricin	Mette	Diagnosis	Case No
1	10	0	100 not clear	1 6 (2 6)	Carcinoma pylorus *	F S
2	40	30	100-200	3 8 (14 4)	Hyperchlorhydria	M ,464
3	42	+	100	3 1 (9 6)	Chr constipation	P , 335
4	43	+	Not made	3 3 (10 9)	Hyperchlorhydria	P , 273
5	44	26	200	3 2 (10 2)	Gastro enteroptosis	M , 505
6	48	10	100	4 9 (24)	Chloro-anemia	M , 311
7	50	18	10	3 9 (15 2)	Chr gastritis	M , 570
8	50	30	200	4 4 (19 4)	Migraine—dilatation of stomach	M , 511
9	50	+	100 not clear	0 5 (0 25)	Pyloric obstruction†	G C
10	50	+	Not made	3 2 (10 2)	Constipation—nervous dyspepsia	P , 300
11	50	+	Not made	4 9 (24 0)	Chr constipation	F B
12	54	34	100-200	4 3 (18 5)	Gastric neurosis	M , 434
13	54	36	100	Not made	Tubercular enteritis	M ,659
14	56	24	100	Not made	Cholecystitis	M , 884
15	58	30	100 not clear	3 7 (13 7)	Hyperchlorhydria	M , 402
16	58	34	100	3 0 (9 0)	Neurasthenia—gastric neurosis	M , 449
17	60	45	100	5 2 (27 0)	Cholecystitis—hyperchlorhydria	M , 791
18	60	+	100	5 0 (25 0)	Malnutrition—chr pancreatitis(?)	S C
19	45	20	100	Not made	Gastric neurosis	M , 663

* Without preliminary lavage Lactic ac + Lowei dilution of 11cin not made
† Probable carcinoma Butyric acid Lowei dilution of 11cin not made

Gioss advances a new method which he claims to be simpler than the
foiegoing His method is based on the piecipitation of undigested casein
by sodium acetate, but we have had no opportunity of studying its value.
Gioss claims that the Jacoby-Solms method is open to criticism on one
point, and that is that the ricin they used is very impuie and that there
is no way of deteimining just what foreign bodies are mixed with it He
also objects to the method on giounds of expense, but this depending
meiely on a peisonal point of view, requires no comment

In making our studies we have followed closely the technic as laid down by Solms and have seen no reason to make any change or modification The only drawback we have encountered is that the ricin solution must be freshly prepared We tried making up a large amount, and filtering it only as needed, but the filtrate was so cloudy that it was difficult to determine the extent of pepsin digestion, as the solution did not become clear even when the gastric juice was but little diluted After the ricin solution is once made, the preparation of the five tubes for peptic digestion occupies very little time, not more than seven minutes on an average, when once the technic has been perfected

The results of our studies are shown in the accompanying tables, which are self-explanatory

SUMMARY OF THE TABLE OF NORMAL ACIDITY (40-60)

Apart from three cases, Nos 1, 9 and 18 the ricin and the Mette methods gave results within normal limits In our table the ricin results of Case 1 is reported as "100 not clear," but in this case, as in Case 9, lower dilutions than 1 100 were not made Finding that 100 was not digested, we should have begun with a dilution of 1 10, when there would doubtless have been a low reading corresponding with that by the Mette method Case 18 shows the Mette result to be at the extreme upper limit of the normal, while the ricin remains exactly normal From a study of the table we see that, apart from those cases with organic acids or diminished free hydrochloric acid, no aid in diagnosis other than that derived from the ordinary chemical examination has been obtained by the determination of pepsin In Case 9 retention, favoring the production of organic acids is the cause of the relatively high acidity The same case (Table 2, 10), after lavage, showed a very low acidity and a minimal amount of pepsin Therapeutically the table is suggestive, but nothing more

SUMMARY OF THE TABLE OF LOW ACIDITY (BELOW 40)

With low acidity the pepsin is also low, both by the ricin and Mette methods In two instances, Cases 8 and 5, the Mette was normal, while the ricin was absent or diminished, respectively This discrepancy can be explained, as the controls for the Mette tests were also high In Case 14 the ricin was normal while the Mette was subnormal We have no explanation to offer for this variation

Pepsin determination seems to be of value in distinguishing simple gastritis and neuroses from achylia and carcinoma In the last two the

pepsin is invariably very much diminished, whereas in the first two it is unaffected or but slightly altered In this we disagree with Witte, who found that pepsin was always low in neuroses

SUMMARY OF THE TABLE OF HYPERACIDITY (ABOVE 60)

With very few exceptions, the ricin and the Mette methods coincided in cases of hyperacidity, although the former is not capable of showing the finer gradations of the latter In two cases, 27 and 55,

TABLE 2—SUBNORMAL ACIDITY—BELOW 40

Serial No	Total Acid	Free Hcl	Ricin	Mette	Diagnosis	Case No
1	35	0	10-20	2 3 (5 3)	Endarteritis—chr tuberculosis	M , 110
2	34	+	Not made	3 4 (11 6)	Constipation—Subacidity	P , 271
3	28	6	10	2 8 (7 8)	Cholelithiasis—gastritis	M 251
4	26	0	20 50	2 0 (4 0)	Polycythemia—chr gastritis*	M , 814
5	26	8	10 20	3 3 (10 9)	Gastric neurosis	M , 579
6	25	0	10	0 8 (0 64)	Pyelitis	M , 189
7	22	0	10	1 0 (1 0)	Chr gastroenteritis†	M , 813
8	22	0	0	3 4 (11 6)	Chr gastritis	M , 571
9	20	0	0	0 1 (0 1)	Anacidity	M , 576
10	12	0	Not made	0 5 (0 25)	Carcinoma pylorus‡	F S
11	12	0	Not made	0 8 (0 64)	Chr Diarrhea—achylia gastrica§	P , 350
12	12	0	Not made	0 5 (0 25)	Incipient tbc —splanchnoptosis achylia gastrica	P , 15
13	4	0	Not made	0	Achylia gastrica‖	P , 270
14	18 (1)	+	100 200	2 4 (5 7)	Spastic stricture of esophagus	P , 302
15	34 (2)	+	100 not clear	2 2 (4 8)	ib**	ib
16	6 (3)	0	10 not clear	0	ib††	ib

* Vomitus
‡ Lactic acid present after lavage See F
§ No lactic acid
** Lower dilution of ricin not made

† Lactic acid present
S , Table 1
‖ Lactic acid present
†† Contents of esophageal dilatation

the ricin was 1,000, while the Mette was also high In Case 37 there was a disproportion between the two methods, the ricin being 1,000 while the Mette showed a normal value In this case two dilutions of ricin were made, one of 1 100 and the other 1 1000, in each of which the result was 1,000 units In two other cases, 53 and 56, the ricin was abnormally high and the Mette low, which can be explained by the low result obtained in the control experiment

Here our efforts to find some diagnostic aid in the quantitative estimation of pepsin have met with failure   The fact that there is no definite relation between the degree of acidity and the amount of pepsin might suggest the use of artificial pepsin in occasional cases

COMPLETE SUMMARY

Our tests indicate that the normal variation of the Mette method is between 3 (9) and 5 (25), of the ricin method 100 to 200   In carcinoma ventriculi, achylia and occasionally in chronic gastritis, the pepsin determination reveals values below the minimal normal, but as a rule in neuroses and chronic gastritis the pepsin is relatively but little affected in contradistinction to carcinoma and achylia, and this would seem to be of assistance in making a differential diagnosis between these conditions We have found, as have others, that within normal limits there are wide variations without apparent relation to the acidity, but at present we are not in a position to draw any diagnostic or therapeutic conclusions from these observations

The results obtained with the ricin method correspond with those shown by the Mette method, that is, normal values and subnormal values are clearly shown, but the finer variations are not seen and when present frequently do not correspond with the Mette results   This is true even when we have made allowance for differences in the Mette tubes by means of the controls referred to above

Both tests are valuable as rough quantitative methods, and they are carried out with equal facility   The Mette has the advantage of excluding variations due to differences in acidity without requiring any previous titration   There has been no attempt made to see whether the ricin method follows the law of Schutz, nor has there been any attempt made to bring the various tubes to a uniform acidity   The variation in the acidity of the five tubes would seem *a priori* to be fruitful of grave errors This could probably be obviated by suitable dilutions with N/20 hydrochloric acid, similar to those employed by Nirenstein and Schiff in their modification of the Mette method   These questions may form the basis of a supplementary communication

We have made little therapeutic use of the knowledge we have obtained   The wide variations in the pepsin values would suggest that the drug has been too much despised by stomach specialists, though this can not be said of practitioners in general   It would seem to be indicated in cases showing subnormal peptic values, with preservation of at least a fair degree of acidity   In chronic gastritis with low acidity and low pepsin, in achylia and in carcinoma it would be necessary to add hydro-

TABLE 3—HYPERACIDITY—ABOVE 60

Serial No	Total Acid	Free Hcl	Ricin	Mette	Diagnosis	Case No
1	62	+	Not made	3 2 (10 2)	Gastric ulcer	P , 310
2	62	+	Not made	3 8 (14 0)	Constipation—chronic gastritis	P , 229
3	62	+	100	4 6 (21 2)	Cholelithiasis—pyloric adhesions	P., 289
4	62	30	100 200	Not made	Goiter—dilated stomach	M 871
5	62	34	100	2 8 (7 8)	Psoriasis—eczema	M 520
6	62	36	100 200	4 1 (16 8)	Gastric neurosis	M , 300
7	62	16	10	3 8 (14 4)	Carcinoma pylorus*	M , 227
8	64	40	100	3 3 (10 9)	Neurosis	M , 575
9	64	30	100	Not made	Nephritis—gastritis	M , 824
10	64	48	100	3 1 (9 6)	Adhesions(?)—hyperchlorhydria	M , 615
11	64	+	Not made	2 3 (5 3)	Chronic gastro enteritis	P , 272
12	65	40	100 200	3 6 (13 0)	Glycosuria	M , 500
13	65	40	100	3 4 (11 6)	Syphilis—neurasthenia	M , 176
14	66	40	100	2 8 (7 8)	Myalgia	M , 680
15	66	36	100	3 2 (10 2)	Tachycardia	M , 236
16	66	40	100	Not made	Gastroptosis—gastric neurosis	M , 225
17	67	+	Not made	3 4 (11 6)	Epilepsy	P , 324
18	68	24	200	3 6 (13 0)	Frontal sinusitis—neurosis—hyperacid	M , 123
19	68	42	200	4 3 (18 5)	Gout—neurosis—alcoholic gastritis ┬	M , 498
20	68	34	100 not clear	3 3 (10 9)	Pancreatitis—hyperchlorhydria	M , 356
21	68	46	100 200	4 6 (21 2)	Cholecystitis—gastric ulcer	M , 322
22	68	+	100	4 0 (16 0)	Hypochondriasis	F W
23	68	+	Not made	3 2 (10 2)	Gastric ulcer	F M
24	68	44	100-200	5 9 (34 8)	Chr appendicitis—gastric neurosis	M , 757
25	70	40	100	Not made	Jaundice—cholecystitis	M , 664
26	70	40	100-200	4 0 (16 0)	Gastritis—hyperchlorhydria	M , 734
27	70	54	1000 •	5 8 (33 6)	Hour glass contraction of stomach—pyloric adhesions	M , 282
28	70	46	100	3 2 (10 2)	Fibroid of uterus—hyperchlorhydria	M , 371
29	73	+	Not made	4 4 (19 4)	Constipation—hyperchlorhydria .	P , 258
30	74	44	100	4 7 (22 0)	Hyperchlorhydria—pylorospasm—cholecystitis—chr appendicitis	M , 335
31	75	55	100	3 0 (9 0)	Hyperchlorhydria	M , 538
32	75	40	100 200	3 0 (9 0)	Exophthalmic goiter	M , 455
23	76	30	100	4 0 (16 0)	Appendicitis	M , 326
34	76	+	Not made	3 0 (9 0)	Splanchnoptosis	S P
35	76	+	Not made	5 4 (29 1)	Gastroptosis—hyperchlorhydria	P , 193

* Vomitus   ┬ Hammerschlag, 97%

TABLE 3—CONTINUED

Serial No	Total Acid	Free Hcl	Ricin	Mette	Diagnosis	Case No
36	78	56	100	3 5 (12 3)	Chr appendicitis	M , 593
37	78	64	1000	3 8 (14 4)	Appendicitis—hyperchlorhydria ‡	M , 476
38	78	36	100	3 9 (15 2)	Hyperchlorhydria	M , 450
39	78	40	100	3 8 (14 4)	Gastric ulcer	M , 430
40	80	+	Not made	4 0 (16 0)	Splanchnoptosis—incipient tbc	P , 296
41	80	55	100	3 4 (11 6)	Hyperchlorhydria	M , 678
42	80	55	100	3 0 (9 0)	Hyperchlorhydria	M , 585
43	82	52	100	3 0 (9 0)	Hyperchlorhydria	T T M
44	82	52	100	3 8 (14 4)	Bronchitis—gastritis	M 599
45	82	+	100	4 6 (21 2)	Cholelithiasis—hyperchlorhydria	F B
46	82	54	100	3 4 (11 6)	Gastritis	M , 689
47	84	52	100	3 1 (9 6)	Hyperchlorhydria	T M B
48	84	60	100	Not made	Neurosis—hyperchlorhydria	M 883
49	85	35	100	2 9 (8 4)	Neurasthenia—gastroptosis	M , 692
50	85	55	100	2 6 (6 8)	Gastric neurosis	M , 667
51	86	48	100	4 9 (24 0)	Gastric neurosis	M , 561
52	86	58	100	5 2 (27 0)	Appendicitis—hyperchlorhydria	M , 273
53	88	54	500	2 8 (7 8)	Cholecystitis—hyperchlorhydria §	M , 171
54	88	58	100-200	4 9 (24 0)	Frontal and ethmoidal sinusitis—hyperacidity	M , 785
55	88	62	1000	5 3 (28 0)	Gastritis—hyperchlorhydria°	M , 334 ,
56	95	60	500	3 1 (9 6)	Neurosis—hyperchlorhydria	M '489
57	100	45	100	2 9 (8 4)	Gastric ulcer	M , 597
58	106	94	100 200	Not made	Cystitis—enteritis	M , 828
59	110	62,	200	3 7 (13 7)	Epilepsy (?)	M , 713
60	112	+	Not made	4 2 (17 6)	Hyperchlorhydria	P , 341

‡ Two controls, first with dil of 1 100 , second with dil of 1 1000
§ Mette control also low

chloric acid In many cases it is doubtful if enough acid could be introduced, except occasionally with a stomach tube, to allow of normal proteolysis A practical expedient (Sailer) is to saturate meat or milk, before taking, with dilute hydrochloric acid until free acid can be detected, after which a small dose of hydrochloric acid will suffice Pepsin should be given in sufficient amounts to make a 1/4 to 1/16 per cent solution in the contents of the stomach (estimated in advance) It should be given with or followed by at least twenty minims of dilute hydrochloric acid Both may be repeated once or twice at short intervals to make up

foi the amount expelled into the duodenum Gasteine, oi the noimal gastiic secietion of the dog obtained thiough a Pavlow fistula, has been advocated by Fiémont and otheis (see Bettmann) in doses of 100 to 500 c c We have had no expeiience with it, but it would seem to have no advantage ovei a mixture of pepsin and hydiochloiic acid unless it possesses some "vital" oi othei piopeity independent of its piincipal constituents

In conclusion, we desiie to acknowledge oui indebtness to Dis Mussei, Sailei and Talley foi the use of theii clinical mateiial which we have fieely used to supplement oui own

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